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(54) Title: MUTATIONS IN ION CHANNELS

(57) Abstract: A method of identifying a subject predisposed to a disorder associated with ion channel dysfunction, comprising ascertaining whether at least one of the genes encoding ion channel subunits in said subject has undergone a mutation event as set forth in one of SEQ ID Numbers: 1-72.

MUTATIONS IN ION CHANNELS

Technical Field

The present invention is concerned with mutations in proteins having biological functions as ion channels and, more particularly, with such mutations where they are associated with diseases such as epilepsy and disorders associated with ion channel dysfunction including, but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic ataxia, migraine, Alzheimer's disease, schizophrenia, Parkinson's disease, anxiety, depression, phobic obsessive hyperekplexia, inflammatory neuropathic pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness and total colour-blindness.

20 Background Art

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Epilepsies constitute a diverse collection of brain disorders that affect about 3% of the population at some time in their lives (Annegers, 1996). An epileptic seizure can be defined as an episodic change in behaviour caused by the disordered firing of populations of neurons in the central nervous system. This results in varying degrees of involuntary muscle contraction and often a loss of consciousness. Epilepsy syndromes have been classified into more than 40 distinct types based upon characteristic symptoms, types of seizure, cause, age of onset and EEG patterns (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). However the single feature that is common to all syndromes is the persistent increase in neuronal excitability that is both occasionally and unpredictably expressed as a seizure.

A genetic contribution to the aetiology of epilepsy has been estimated to be present in approximately 40% of

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affected individuals (Gardiner, 2000). As epileptic seizures may be the end-point of a number of molecular aberrations that ultimately disturb neuronal synchrony, genetic basis for epilepsy is likely heterogeneous. There are over 200 Mendelian diseases which include epilepsy as part of the phenotype. diseases, seizures are symptomatic of underlying neurological involvement such as disturbances in brain structure or function. In contrast, there are also a number of "pure" epilepsy syndromes in which epilepsy is the sole manifestation in the affected individuals. These are termed idiopathic and account for over 60% of all epilepsy cases.

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Idiopathic epilepsies have been further divided into partial and generalized sub-types. Partial (focal or local) epileptic fits arise from localized cortical discharges, so that only certain groups of muscles are involved and consciousness may be retained. However, in generalized epilepsy, EEG discharge shows no focus such that all subcortical regions of the brain are involved. Although the observation that generalized epilepsies are frequently inherited is understandable, the mechanism by which genetic defects, presumably expressed constitutively in the brain, give rise to partial seizures is less clear.

The molecular genetic era has resulted in spectacular advances in classification, diagnosis and biological understanding of numerous inherited neurological disorders including muscular dystrophies, familial neuropathies and spinocerebellar degenerations. These disorders are all uncommon or rare and have simple Mendelian inheritance. In contrast, common neurological diseases like epilepsy, have complex inheritance where they are determined by multiple genes sometimes interacting with environmental influences. Molecular genetic advances in disorders with complex inheritance have been far more modest to date (Todd, 1999).

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Most of the molecular genetic advances have occurred by a sequential three stage process. First a clinically homogeneous disorder is identified and its inheritance determined. Second, linkage analysis performed on carefully characterized clinical populations with the disorder. Linkage analysis is a process where the localization of a particular disorder chromosomal narrowed down to approximately 0.5% of the total genome. Knowledge of linkage imparts no intrinsic biological insights other than the important clue as to where to look in the genome for the abnormal gene. Third, strategies such as positional cloning or the positional candidate approach are used to identify the aberrant gene and its specific mutations within the linked region (Collins, 1995).

Linkage studies in disorders with complex inheritance have been bedevilled by negative results and by failure to replicate positive findings. A sense of frustration permeates current literature in the genetics of complex disorders. Carefully performed, large scale involving hundreds of sibpairs in disorders including multiple sclerosis and diabetes have been essentially negative (Bell and Lathrop, 1996; Lernmark and Ott, 1998). An emerging view is that such disorders are due to the of many genes small effect ο£ identification of these genes may only be possible with very large-scale association studies. Such studies on a genome-wide basis are currently impossible to incomplete marker sets and computational limitations.

The idiopathic generalized epilepsies (IGE) are the most common group of inherited human epilepsy and do not have simple inheritance. Like other complex disorders, linkage studies in IGE have generated controversial and conflicting claims. Previous authors have suggested the possibility of multifactorial, polygenic, oligogenic or two locus models for the disease (Andermann, 1982; Doose

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and Baier, 1989; Greenberg et al., 1988a; 1992; Janz et al., 1992).

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Two broad groups of IGE are now known - the classical idiopathic generalized epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and the newly recognized genetic syndrome of generalized epilepsy with febrile seizures plus (GEFS⁺) (Scheffer and Berkovic, 1997; Singh et al., 1999).

10 The classical IGEs are divided into a number of clinically recognizable but overlapping sub-syndromes including childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy etc (Commission on Classification and Terminology of the International League 15 Against Epilepsy, 1989; Roger et al., 1992). The syndromes are identified by age of onset and the pattern of seizure types (absence, myoclonus and tonic-clonic). patients, particularly those with tonic-clonic seizures alone do not fit a specifically recognized sub-20 syndrome. Arguments for regarding these as separate syndromes, yet recognizing that they are part of a neurobiological continuum, have been presented previously (Berkovic et al. 1987; 1994; Reutens and Berkovic, 1995).

GEFS⁺ was originally recognized through large multigeneration families and comprises a variety of subsyndromes. Febrile seizures plus (FS⁺) is a sub-syndrome where children have febrile seizures occurring outside the age range of 3 months to 6 years, or have associated febrile tonic-clonic seizures. Many family members have a phenotype indistinguishable from the classical febrile convulsion syndrome and some have FS⁺ with additional absence, myoclonic, atonic, or complex partial seizures. The severe end of the GEFS⁺ spectrum includes myoclonicastatic epilepsy.

The cumulative incidence for epilepsy by age 30 years (proportion suffering from epilepsy at some time) is 1.5% (Hauser et al., 1993). Accurate estimates for the

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cumulative incidence of the IGEs are unavailable. epidemiological studies where attempts are to subclassify epilepsies, rather few cases of IGE are diagnosed, and many cases are unclassified. probably because cases are rarely directly examined by epileptologists. In clinic- or office-based series seen by experts, most cases are classifiable and IGEs account for about 25% of cases. This suggests that about 0.3% of the population suffer from IGE at some time.

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10 In outbred populations many patients with classical IGE appear to be sporadic as siblings and parents are usually unaffected. Systematic EEG studies on clinically unaffected family members show an increase dependent occurrence ο£ generalized epileptiform 15 discharges compared to controls. In addition, approximate 0.3% of the population with clinical systematic EEG studies suggest that about 1% of healthy children have generalized epileptiform discharges while awake (Cavazzuti et al., 1980; Okubo et al., 1994).

Approximately 5-10% of first degree relatives classical IGE probands have seizures with affected relatives usually having IGE phenotypes or febrile seizures. While nuclear families with 2-4 individuals are well recognized and 3 generation families or grandparent-grandchild pairs are occasionally observed (Italian League Against Epilepsy Genetic Collaborative Group, 1993), families with multiple affected individuals extending over 4 or more generations are exceptionally rare.

For GEFS⁺, however, a number of large multi-generation families showing autosomal dominant inheritance with incomplete penetrance are known. Similar to classical IGE, analysis of sporadic cases and small families with GEFS⁺ phenotypes does not suggest simple Mendelian inheritance.

Indeed, bilineal inheritance, where there is a history of epilepsy on maternal and paternal sides, is observed in both GEFS⁺ and classical IGE families (Singh et al., 1999;

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Italian League Against Epilepsy Genetic Collaborative Group, 1993).

Within single families with classical IGE or GEFS+, affected individuals often have different sub-syndromes. The closer an affected relative is to the proband, the more similar are their sub-syndromes, and siblings often similar sub-syndromes (Italian League Against Epilepsy Genetic Collaborative 1993). Group, commonly, families are observed where most, or all, known affected individuals have one classical IGE sub-syndrome such as childhood absence epilepsy or juvenile myoclonic epilepsy (Italian Leaque Against Epilepsy Collaborative Group, 1993).

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Importantly, sub-syndromes are identical in affected monozygous twins with IGE. In contrast, affected dizygous twins, may have the same or different sub-syndromes. Classical IGE and GEFS⁺ sub-syndromes tend to segregate separately (Singh et al., 1999).

In some inbred communities, pedigree analysis strongly recessive inheritance suggests for juvenile myoclonic epilepsy and other forms of IGE (Panayiotopoulos and Obeid, 1989; Berkovic et al., 2000). In such families, sub-syndromes are much more similar in affected siblings in affected sib-pairs from outbred families. Recently, a family with an infantile form of IGE with autosomal recessive inheritance, confirmed by linkage analysis, was described in Italy (Zara et al., 2000).

Most work on the molecular genetics of classical IGEs has been done on the sub-syndrome of juvenile myoclonic epilepsy where a locus in proximity or within the HLA region on chromosome 6p was first reported in 1988 (Greenberg et al., 1988b). This finding was supported by two collaborating laboratories, in separate patient samples, and subsequently three groups provided further evidence for a 6p locus for juvenile myoclonic epilepsy in some, but not all, of their families. However, genetic defects have not been found and the exact locus of the

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gene or genes, in relationship to the HLA region, remains controversial. Strong evidence for linkage to chromosome 6 also comes from a study of a single large family with juvenile myoclonic epilepsy, but in this pedigree the locus is well outside the HLA region. A locus on chromosome 15q has also been suggested for juvenile myoclonic epilepsy, but was not confirmed by two other studies.

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In general, the results of studies of the putative chromosomal 6p locus in the HLA region in patients with absence epilepsies or other forms of idiopathic generalized epilepsies have been negative. The major exception is that study of probands with tonic-clonic seizures on awakening, a sub-syndrome closely related to juvenile myoclonic epilepsy, suggests linkage to 6p.

Linkage for classical remitting childhood absence epilepsy remains elusive, but in a family with persisting absence evolving into a juvenile myoclonic phenotype, linkage to chromosome 1p has been claimed. An Indian pedigree with persisting absence and tonic-clonic seizures may link to 8q24. Linkage to this region was also by a non-parametric analysis in IGE, irrespective of subsyndrome, but was not confirmed in another study. Other loci for IGEs that have been reported in single studies include 3p14, 8p, 18 and possibly 5p. The unusual example of recessively inherited infantile onset IGE described in Italy maps to 16p in a single family.

Thus, like most disorders with complex inheritance, the literature on genetics of classical IGEs is confusing and contradictory. Some, and perhaps much, of this confusion is due to heterogeneity, with the likelihood of a number of loci for IGEs. The studies reviewed above were principally performed on multiple small families, so heterogeneity within and between samples is probable. Whether all, some, or none of the linkages reported above will be found to harbour relevant genes for IGE remains to

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be determined. Most of the studies reviewed above used analysis methods assuming Mendelian inheritance, an assumption that is not correct for outbred communities. Some studies used multiple models (autosomal recessive, autosomal dominant). Although parametric linkage analysis may be reliable in some circumstance of analyzing complex disease, it can lead to spurious findings as highlighted by the literature on linkage in major psychoses (Risch and Botstein, 1996).

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In so far as GEFS⁺ is concerned, linkage analysis on rare multi-generation large families with clinical dominant gene of major autosomal evidence a demonstrated loci on chromosomes 19q and 2q. Both the 19q and 2q GEFS+ loci have been confirmed in independently ascertained large families, and genetic defects have been identified. Families linked to 19q are known and a mutation in the gene for the $\beta 1$ subunit of the neuronal sodium channel (SCN1B) has been identified (Wallace et al., 1998). This mutation results in the loss of a critical disulphide bridge of this regulatory subunit and causes a loss of function in vitro. Families linked to 2q are also known and mutations in the pore-forming α subunit the neuronal sodium channel (SCN1A) have identified (PCT/AU01/01648; Wallace et al., 2001b; Escayq et al., 2000). Studies on the more common small families with GEFS⁺ have not revealed these or other mutations to date.

In addition to the SCN1B and SCN1A mutations in GEFS⁺, four other gene defects have been discovered for human idiopathic epilepsies through the study of large families. Mutations in the alpha-4 subunit of the neuronal nicotinic acetylcholine receptor (CHRNA4) occur in the focal epilepsy syndrome of autosomal dominant nocturnal frontal lobe epilepsy (Australian patent AU-B-56247/96; Steinlein et al., 1995). Mutations in the gamma-2 subunit of the GABAA receptor (GABRG2) have been identified in childhood absence epilepsy, febrile seizures (including febrile

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seizures plus) and myoclonic epilepsy (PCT/AU01/00729; Wallace et al., 2001a). Finally, mutations in two potassium channel genes (KCNQ2 and KCNQ3) were identified in benign familial neonatal convulsions (Singh et al., 1998; Biervert et al., 1998; Charlier et al., 1998). Although initially regarded as a special form of IGE, this unusual syndrome is probably a form of inherited focal epilepsy.

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Further to these studies, mutations in other genes have been identified to be causative of epilepsy. These include mutations in the beta-2 subunit (CHRNB2) of the neuronal nicotinic acetylcholine receptor (PCT/AU01/00541; Phillips et al., 2001) and the delta subunit (GABRD) of the GABAA receptor (PCT/AU01/00729).

A number of mouse models approximating human IGE are known. These mice mutants have ataxia in addition to generalized spike-and-wave discharges with absences or tonic-clonic seizures. Recessive mutations in calcium channel subunit genes have been found in lethargic (CACNB4), tottering/leaner (CACNA1A), and stargazer (CACNG2) mutants. The slow-wave epilepsy mouse mutant has a mutation in the sodium/hydrogen exchanger gene, which may have important downstream effects on pH-sensitive ion channels.

The human and mouse literature is now suggesting that 25 the idiopathic epilepsies comprise a family channelopathies with mutations in ion channel subunits of voltage-gated (eg SCN1A, SCN1B, KCNQ2, KCNQ3) or ligandgated (eg CHRNA4, CHRNB2, GABRG2, GABRD) types. 30 channels are typically comprised of a number of subunits, specified by different chromosomes. genes onstoichiometry and conformation of ion channel subunits are not yet well understood, but many have multiple subunits in a variety of combinations.

The involvement of ion channels in other neuro/physiological disorders has also been observed (reviewed in Dworakowska and Dolowy, 2000). Mutations in

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voltage-gated sodium, potassium, calcium and chloride channels as well as ligand-gated channels such as the acetylcholine and GABA receptors may lead to physiological disorders such as hyper- and hypo-kalemic paralysis, myotonias, malignant hyperthermia, myasthenia and cardiac arrhythmias. Neurological disorders other than epilepsy that are associated with ion channel mutations include episodic ataxia, migraine, Alzheimer's disease, Parkinson's schizophrenia, disease, hyperekplexia, anxiety, depression, phobic obsessive symptoms, as well as neuropathic pain, inflammatory pain and chronic/acute pain. Some kidney disorders such as Bartter's syndrome, polycystic kidney disease and Dent's disease, secretion disorders such as hyperinsulinemic hypoglycemia of infancy and cystic fibrosis, and vision disorders such

congenital stationary night blindness and total colourblindness may also be linked to mutations in ion channels.

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Disclosure of the Invention

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- In a new genetic model for the idiopathic generalised epilepsies (IGEs) described in PCT/AU01/00872 (the disclosure of which is incorporated herein by reference) it has been postulated that most classical IGE and GEFS+ cases are due to the combination of two mutations in multi-subunit ion channels. These are typically point mutations resulting in a subtle change of function. The critical postulate is that two mutations, usually, but not exclusively, in different subunit alleles ("digenic model"), are required for clinical expression of IGE. It was further proposed that
 - a) A number of different mutated subunit pairs can be responsible for IGE. Combinations of two mutated subunits lead to an IGE genotype with ~30% penetrance.
- b) The total allele frequency of mutated subunits is ~8%. It was calculated that approximately 15% of the population has one or more mutated

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subunit genes and 1% have two or more mutated subunits.

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- c) Sub-syndromes are principally determined by the specific combination of mutated subunit pairs, although one or more other genes, including ion channel subunits, of smaller effect may modify the phenotype.
- d) Mutated subunit combinations that cause classical IGEs are largely separate from those that cause GEFS⁺, although some subunits may be involved in both syndromes.
- e) Individuals with single 'change of function' mutations would not have IGE, but such mutations may contribute to simple febrile seizures, which are observed with increased frequency in relatives of IGE probands.

The model also proposes that subunit mutations with severe functional consequences (eg breaking disulphide bridge in SCN1B or amino acid substitution in the pore forming regions of SCN1A for GEFS+) cause autosomal dominant generalized epilepsies with penetrance of 60-90%. The precise sub-syndromes in ${\tt GEFS}^+$ are determined by minor allelic variation or mutations in other ion channel subunits. Such "severe" mutations are rare (allele frequency <0.01%) and are infrequent causes of GEFS⁺. They very rarely, or perhaps never, cause classical IGE.

The identification of molecular changes in ion channel subunits is therefore a significant step towards the elucidation of genetic variants that alone or in combination (based on the digenic model) give rise to an epilepsy phenotype, and to other neuro/physiological disorders associated with ion channel dysfunction.

The present inventors have identified a number of novel mutations or variants in genes encoding subunits of ion channels in individuals with epilepsy. It will be appreciated that for each molecular defect one can provide

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an isolated nucleic acid molecule coding for a protein having a biological function as part of an ion channel in a mammal, wherein a mutation event selected from the group consisting of point mutations, deletions, insertions and rearrangements has occurred so as to affect the functioning of the ion channel. In some instances this single mutation alone will produce a phenotype of epilepsy or other neuro/physiological disorders associated with ion channel dysfunction.

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In the case where a single mutation alone does not say, an epilepsy phenotype, there would be provided one or more additional isolated nucleic acid molecules coding for proteins having a biological function as part of an ion channel in a mammal, wherein a mutation event selected from the group consisting of mutations, deletions, insertions and rearrangements has occurred so as to affect the functioning of the channel. The cumulative effect of the mutations in each isolated nucleic acid molecule in vivo is to produce a epilepsy or another neuro/physiological disorders in said mammal. The mutations may be in nucleic acid molecules coding for protein subunits belonging to the same ion channel or may be in nucleic acid molecules coding for protein subunits that belong to different ion channels.

Typically such mutations are point mutations and the ion channels are voltage-gated channels such as a sodium, potassium, calcium or chloride channels or are ligand-gated channels such as members of the nAChR/GABA super family of receptors, or a functional fragment or homologue thereof.

Mutations may include those in non-coding regions of the ion channel subunits (eg mutations in the promoter region which affect the level of expression of the subunit gene, mutations in intronic sequences which affect the correct splicing of the subunit during mRNA processing, or mutations in the 5' or 3' untranslated regions that can affect translation or stability of the mRNA). Mutations

may also and more preferably will be in coding regions of the ion channel subunits (eg nucleotide mutations may give rise to an amino acid change in the encoded protein or nucleotide mutations that do not give rise to an amino acid change but may affect the stability of the mRNA).

Mutation combinations may be selected from, but are not restricted to, those identified in Table 1.

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Accordingly in one aspect of the present invention there is provided a method of identifying a subject predisposed to a disorder associated with ion channel dysfunction, comprising ascertaining whether at least one of the genes encoding ion channel subunits in said subject has undergone a mutation event selected from the group consisting of the mutation events set forth in the following Table:

Subunit Exon/Intron DNA Mutation Gene SCN1A Exon 5 c664C→T SCN1A Exon 8 c1152G→A SCN1A Exon 9 c1183G→C SCN1A Exon 9 c1207T→C SCN1A Exon 9 $c1237T\rightarrow A$ SCN1A Exon 9 $c1265T\rightarrow A$ SCN1A Exon 21 $c4219C \rightarrow T$ SCN1A Exon 26 c5339T→C SCN1A Exon 26 $c5674C \rightarrow T$ SCN1B Exon 3 $c254G \rightarrow A$ SCN2A Exon 6A c668G→A SCN2A Exon 16 $c2674G \rightarrow A$ SCN2A Exon 17 c3007C→A SCN2A Exon 19 c3598A→G Exon 20 SCN2A c3956G→A SCN2A Exon 12 c1785T→C SCN2A Exon 27 $c4919T \rightarrow A$ SCN1A Intron 9 IVS9-1G→A SCN1A Intron 23 IVS23+33G→A SCN2A Intron 7 IVS7+61T \rightarrow A SCN2A Intron 19 IVS19-55A→G SCN2A Intron 22 IVS22-31A→G SCN2A Intron 2 IVS2-28G→A SCN2A Intron 8 IVS8-3T \rightarrow C SCN2A Intron 11 IVS11+49A \rightarrow G SCN2A Intron 11 IVS11-16C \rightarrow T

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SCN2A	Intron 17	IVS17-71C→T	
SCN2A SCN2A	Intron 17 Intron 17	IVS17-74delG IVS17-74insG	
CHRNA5	Exon 4	C400G→A	
CHRNA2	Exon 4	C400G→A C373G→A	
CHRNA3	Exon 2		
CHRNA2	Exon 4	c110G→A	
CHRNA2	Exon 5	c351C→T	
		c771C→T	
CHRNA3	Exon 2	c159A→G	
CHRNA3	Exon 4	c291G→A	
CHRNA3	Exon 4	c345G→A	
CHRNA2	Intron 3	IVS3-16C→T	
CHRNA3	Intron 3	IVS3-5T→C	
CHRNA3	Intron 4	IVS4+8G→C	
KCNQ2	Exon 1	c204-c205insC	
KCNQ2	Exon 1	c1A→G	
KCNQ2	Exon 1	c2T→C	
KCNQ2	Exon 8	c1057C→G	
KCNQ2	Exon 11	c1288C→T	
KCNQ2	Exon 14	c1710A→T	
KCNQ2	Exon 15	c1856T→G	
KCNQ2	Intron 9	IVS9+(46-48)de1CCT	
KCNQ3	Intron 11	IVS11+43G→A	
KCNQ3	Intron 12	IVS12+29G→A	
GABRB1	Exon 5	c508C→T	
GABRB1	Exon 9	c1329G→A	
GABRB1	Exon 8	c975C→T	
GABRG3	Exon 8	c995 T→ C	
GABRA1	5' UTR	c-142A→G	
GABRA1	5' UTR	c−31C→T	
GABRA2	3' UTR	c1615G→A	
GABRA5	5' UTR	c-271G→C	
GABRA5	5' UTR	c-228A→G	
GABRA5	5' UTR	c-149G→C	
GABRB2	5' UTR	c-159C→T	
GABRB2	3' UTR	c1749C→T	
GABRPi	5' UTR	$c-101C \rightarrow T$	
GABRB1	Intron 1	IVS1+24T→G	
GABRB1	Intron 6	IVS6+72T→G	
GABRB1	Intron 7	IVS7-34A→G	
GABRB3	Intron 1	IVS1-14C→T	
GABRB3	Intron 7	IVS7+58delAA	
GABRD	Intron 6	IVS6+132insC	
GABRD	Intron 6	IVS6+130insC	
GABRD	Intron 6	IVS6+73delCGCGCCCACCGCCCCTTCCGCG	
GABRG3	Intron 8	IVS8-102C→T	

In a further aspect there is provided a method of identifying a subject predisposed to a disorder associated with ion channel dysfunction, comprising ascertaining whether at least one of the genes encoding ion channel subunits in said subject has undergone a mutation event as set forth in one of SEQ ID Numbers: 1-72.

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In another aspect of the present invention there is provided an isolated nucleic acid molecule encoding a mutant or variant ion channel subunit wherein a mutation event selected from the group consisting of the mutation events set forth in the following Table:

events set	forth in the	Iollowing Table:
Subunit Gene	Exon/Intron	DNA Mutation
SCN1A	Exon 5	
SCN1A	Exon 8	c1152G→A
SCN1A	Exon 9	c1183G→C
SCN1A	Exon 9	c1207T→C
SCN1A	Exon 9	c1237 T→ A
SCN1A	Exon 9	c1265T→A
SCN1A	Exon 21	c4219C→T
SCN1A	Exon 26	c5339 T→ C
SCN1A	Exon 26	c5674C→T
SCN1B	Exon 3	c254G→A
SCN2A	Exon 6A	c668G→A
SCN2A	Exon 16	c2674G→A
SCN2A	Exon 17	c3007C→A
SCN2A	Exon 19	c3598A→G
SCN2A	Exon 20	c3956G→A
SCN2A	Exon 12	c1785 T→ C
SCN2A	Exon 27	c4919T→A
SCN1A	Intron 9	IVS9-1G→A
SCN1A	Intron 23	IVS23+33G→A
SCN2A	Intron 7	IVS7+61T→A
SCN2A	Intron 19	IVS19-55A→G
SCN2A	Intron 22	IVS22-31A→G
SCN2A	Intron 2	IVS2-28G→A
SCN2A	Intron 8	IVS8-3T→C
SCN2A	Intron 11	IVS11+49A→G
SCN2A	Intron 11	IVS11-16C→T
SCN2A	Intron 17	IVS17-71C→T
SCN2A	Intron 17	IVS17-74delG
SCN2A	Intron 17	IVS17-74insG
CHRNA5	Exon 4	c400G→A
CHRNA2	Exon 4	c373G→A

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CHRNA3 Exon 2 c110G \rightarrow A CHRNA2 Exon 4 c351C \rightarrow T CHRNA2 Exon 5 c771C \rightarrow T CHRNA3 Exon 2 c159A \rightarrow G	
CHRNA2 Exon 5 $c771C \rightarrow T$	
CHDNA2	
0111111111	
CITATA A	
CLDN73 CZ9IG→A	
CHDN72 Tobacc 2	
1 ∧22-1 0C→1.	
CHRNA3 Intron 3 IVS3-5T→C CHRNA3 Intron 4	
1√54+8G→C	
VCNO2 Even 1	
ECIA-7G	
ECNO2	
VCNO2 Even 11	
VCNO2	
KCNO2 From 15	
CT0201—2d	
VCNO2 Introd 11	
VCNO2 Total 10	
CARDRI Buch F	
CAPPE1 Even 0	
CADDD1 Etter 0	
CAPDC3 E	
CAPPA1 E/ IMP	
CADDA1 E/ IMD	
CARDAS SA SIMP	
CADDAE EVITED	
CAPDAS 5/ TIMB	
CADDA5 5/ HMD	
C_T23C→T	
CARREL 1	
CADDD1 Tataon C	
CARRA 7	
CABBB2 Tatas 1	
TVST-14C→T	
GABRB3 Intron 7 IVS7+58delAA	
GABRD Intron 6 IVS6+132insC	
GABRD Intron 6 IVS6+130insC	
GABRD Intron 6 IVS6+73delCGCGCCCACCGCCCCTTCCGC	G
GABRG3 Intron 8 IVS8-102C→T	

has occurred.

In still another aspect of the present invention there is provided an isolated nucleic acid molecule encoding a mutant or variant ion channel subunit wherein a WO 2005/014863 - 17 -

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mutation event has occurred as set forth in one of SEQ ID Numbers: 1-72.

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The mutation event disrupts the functioning of an ion channel so as to produce a phenotype of epilepsy, and/or one or more other disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic migraine, Alzheimer's disease, Parkinson's ataxia, hyperekplexia, schizophrenia, disease, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, kidnev disease, Dent's polycystic hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness and total colourblindness, either alone or in combination with one or more additional mutations or variations in the ion channel subunit genes.

In another aspect of the present invention there is provided an isolated nucleic acid molecule encoding a mutant KCNQ2 subunit, wherein the mutation event has occurred in the C-terminal domain of the KCNQ2 subunit and leads to a disturbance in the calmodulin binding affinity of the subunit, so as to produce an epilepsy phenotype.

In one form of the invention, the mutations are in exon 8 or exon 15 of the KCNQ2 subunit and result in the replacement of an arginine residue with a glycine residue at amino acid position 353, or the replacement of a leucine residue with an arginine at amino acid position 619. The R353G mutation occurs as a result of a C to G nucleotide substitution at position 1057 of the KCNQ2 coding sequence as shown in SEQ ID NO: 44. The L619R mutation occurs as a result of a T to G nucleotide substitution at position 1856 of the KCNQ2 coding sequence as shown in SEQ ID NO: 47.

In a further form of the invention, the mutations are in exon 11 or exon 14 of the KCNQ2 subunit and result in

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the replacement of an arginine residue with a stop codon at amino acid position 430, or the replacement of an arginine residue with a serine at amino acid position 570. The R430X mutation occurs as a result of a C to T nucleotide substitution at position 1288 of the KCNQ2 coding sequence as shown in SEQ ID NO: 45. The R570S mutation occurs as a result of an A to T nucleotide substitution at position 1710 of the KCNQ2 coding sequence as shown in SEQ ID NO: 46.

Preferably these mutations create a phenotype of benign familial neonatal seizures (BFNS).

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In a further aspect of the present invention there is provided a combination of two or more isolated nucleic acid molecules each having a novel mutation event as laid out in Table 1. The cumulative effect of the mutations in each isolated nucleic acid molecule *in vivo* is to produce an epilepsy or another disorder associated with ion channel dysfunction as described above in said mammal.

In a particularly preferred embodiment of the present invention, the isolated nucleic acid molecules have a nucleotide sequence as shown in any one of SEQ ID Numbers: 1-72. The sequences correspond to the novel DNA mutations or variants laid out in Table 1.

In another aspect of the present invention there is provided an isolated nucleic acid molecule comprising any one of the nucleotide sequences set forth in SEQ ID Numbers: 1-72.

In another aspect of the present invention there is provided an isolated nucleic acid molecule consisting of any one of the nucleotide sequences set forth in SEQ ID Numbers: 1-72.

The nucleotide sequences of the present invention can be engineered using methods accepted in the art for a variety of purposes. These include, but are not limited to, modification of the cloning, processing, and/or expression of the gene product. PCR reassembly of gene fragments and the use of synthetic oligonucleotides allow

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the engineering of the nucleotide sequences of the present invention. For example, oligonucleotide-mediated site-directed mutagenesis can introduce further mutations that create new restriction sites, alter expression patterns and produce splice variants etc.

As a result of the degeneracy of the genetic code, a number of polynucleotide sequences, some that may have minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention includes each and every possible variation of a polynucleotide sequence that could be made by selecting combinations based on possible codon choices. combinations are made in accordance with standard triplet genetic code as applied the polynucleotide sequences of the present invention, and all such variations are to be considered as being specifically disclosed.

The nucleic acid molecules of this invention typically DNA molecules, and include cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense antisense strands, and may be chemically or biochemically may contain non-natural or modified, orderivatised nucleotide bases as will be appreciated by those skilled modifications the art. Such include labels, intercalators, alkylators methylation, and modified linkages. In some instances it may be advantageous to produce nucleotide sequences possessing a substantially different codon usage than that of the polynucleotide sequences of the present invention. For example, codons may be selected to increase the rate of expression of the peptide in a particular prokaryotic or eukaryotic host corresponding with the frequency that particular codons are utilized by the host. Other reasons to alter the nucleotide sequence without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater halfWO 2005/014863 PCT/AU2004/001051
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life, than transcripts produced from the naturally occurring mutated sequence.

The invention also encompasses production of nucleic acid sequences of the present invention entirely by synthetic chemistry. Synthetic sequences may be inserted into expression vectors and cell systems that contain the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements may include regulatory sequences, promoters, 5' and 3' untranslated regions and specific initiation signals (such as an ATG initiation codon and Kozak consensus sequence) which allow more efficient translation of sequences encoding the polypeptides of the present invention. In cases where the complete coding sequence, including the initiation codon and upstream regulatory sequences, are inserted into the appropriate expression vector, additional control signals may not be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals as described above should be provided by the vector. Such signals may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used (Scharf et al., 1994).

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The invention also includes nucleic acid molecules that are the complements of the sequences described herein.

The present invention allows for the preparation of purified polypeptide or protein from the polynucleotides of the present invention, or variants thereof. In order to do this, host cells may be transformed with a novel nucleic acid molecule as described above, or with nucleic acid molecules encoding two or more mutant ion channel subunits. If the mutant subunits form a part of the same ion channel a receptor protein containing two or more mutant subunits may be isolated. If the mutant subunits are subunits of different ion channels the host cells will

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express two or more mutant receptor proteins. Typically said host cells are transfected with an expression vector comprising a DNA molecule according to the invention or, in particular, DNA molecules encoding two or more mutant ion channel subunits. A variety of expression vector/host systems may be utilized to contain and express sequences encoding polypeptides of the invention. These include, but limited to, microorganisms such as transformed with plasmid or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; cell systems infected with viral expression vectors (e.g., baculovirus); or mouse or other animal or human tissue cell systems. Mammalian cells can also be used to express a protein using a vaccinia virus expression system. invention is not limited by the host cell or vector employed.

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The polynucleotide sequences, or variants thereof, of the present invention can be stably expressed in cell lines to allow long term production of recombinant proteins in mammalian systems. Sequences encoding polypeptides of the present invention can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. The selectable marker confers resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode a protein may be designed to contain signal sequences which direct secretion of the protein through a prokaryotic or eukaryotic cell membrane.

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In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences to process the expressed protein in the fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, glycosylation, phosphorylation, and acylation. Post-translational cleavage of a "prepro" form of the protein may also be specify protein targeting, folding, activity. Different host cells having specific cellular machinery and characteristic mechanisms for translational activities (e.g., CHO or HeLa cells), available from the American Type Culture Collection (ATCC) and may be chosen to ensure the correct modification and processing of the foreign protein.

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When large quantities of the protein product of the gene are needed, such as for antibody production, vectors which direct high levels of expression of this protein may be used, such as those containing the T5 or T7 inducible bacteriophage promoter. The present invention also includes the use of the expression systems described above in generating and isolating fusion proteins which contain important functional domains of the protein. These fusion proteins are used for binding, structural and functional studies as well as for the generation of appropriate antibodies.

In order to express and purify the protein as a fusion protein, the appropriate cDNA sequence is inserted a vector which contains a nucleotide peptide encoding another (for example, glutathionine succinyl transferase). The fusion protein is expressed and recovered from prokaryotic or eukaryotic cells. The fusion protein can then be purified by affinity chromatography based upon the fusion vector sequence. The desired protein is then obtained by enzymatic cleavage of the fusion protein.

Fragments of the polypeptides of the present invention may also be produced by direct peptide synthesis

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using solid-phase techniques. Automated synthesis may be achieved by using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Various fragments of this protein may be synthesized separately and then combined to produce the full-length molecule.

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The present invention is also concerned with polypeptides having a biological function as an ion channel in a mammal, wherein a mutation event selected from the group consisting of substitutions, deletions, truncations, insertions and rearrangements has occurred so as to affect the functioning of the ion channel. In some instances this single mutation alone will produce an epilepsy phenotype or other neuro/physiological disorders associated with ion channel dysfunction.

In the case where a single mutation alone does not say, an epilepsy phenotype, there would be produce, additional isolated provided one more mammalian orpolypeptides having biological functions as part of an ion channel in a mammal, wherein a mutation event selected from the group consisting of substitutions, deletions, truncations, insertions and rearrangements has occurred so as to affect the functioning of the ion channel. effect of the mutations in each cumulative mammalian polypeptide in vivo being to produce epilepsy or another neuro/physiological disorder in said mammal. The mutations may be in polypeptide subunits belonging to the same ion channel as described above, but may also be in ion polypeptide subunits that belong to different channels.

Typically the mutation is an amino acid substitution and the ion channel is a voltage-gated channel such as a sodium, potassium, calcium or chloride channel or a ligand-gated channel such as a member of the nAChR/GABA super family of receptors, or a functional fragment or homologue thereof.

Mutation combinations may be selected from, but are not restricted to, those represented in Table 1.

Accordingly, in a further aspect of the present invention there is provided an isolated polypeptide, said polypeptide being a mutant or variant ion channel subunit wherein a mutation event selected from the group consisting of the mutation events set forth in the following Table:

g	rabre:	
	Subunit	Amino Acid Change
_	Gene	Tanario Tioad Ondrigo
	SCN1A	R222X
	SCN1A	W384X
	SCN1A	A395P
	SCN1A	F403L
	SCN1A	Y413N
	SCN1A	V422E
	SCN1A	R1407X
	SCN1A	M1780T
	SCN1A	R1892X
	SCN1B	R85H
	SCN2A	R223Q
	SCN2A	V892I
	SCN2A	L1003I
	SCN2A	T1200A
	SCN2A	R1319Q
	CHRNA5	V134I
	CHRNA2	A125T
	CHRNA3	· R37H
	KCNQ2	K69fsX119
	KCNQ2	M1V
	KCNQ2	MlT
	KCNQ2	R353G
	KCNQ2	R430X
	KCNQ2	R570S
	KCNQ2	L619R

has occurred.

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In a further aspect of the invention there is provided an isolated polypeptide, said polypeptide being a mutant or variant ion channel subunit wherein a mutation event has occurred such that the polypeptide has the amino acid sequence set forth in one of SEQ ID Numbers: 73-95. The mutation event disrupts the functioning of an ion channel so as to produce a phenotype of epilepsy, and/or one or more other disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic

ataxia, migraine, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis,

congenital stationary night blindness and total colour-

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blindness.

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In a particularly preferred embodiment of the present invention, the isolated polypeptide has an amino acid sequence as shown in any one of SEQ ID Numbers: 73-95. The sequences correspond to the novel amino acid changes laid out in Table 1 for those instances where the DNA mutation results in an amino acid change.

According to still another aspect of the present invention there is provided an isolated polypeptide, said polypeptide being a mutant KCNQ2 subunit, wherein the mutation event has occurred in the C-terminal domain of the KCNQ2 subunit and leads to a disturbance in the calmodulin binding affinity of the subunit, so as to produce an epilepsy phenotype.

In one form of the invention the mutations are substitutions in which an arginine residue is replaced with a glycine residue, or a leucine residue is replaced with an arginine. Preferably the substitutions are R353G and L619R transitions as illustrated by SEQ ID NOS: 92 and 95 respectively.

In a further form of the invention the mutations result in the replacement of an arginine for a stop codon, or an arginine is replaced with a serine. Preferably the mutations are R430X and R570S transitions as illustrated by SEQ ID NOS: 93 and 94 respectively.

In a still further aspect of the present invention there is provided a combination of two or more isolated polypeptides each having a novel mutation event as laid out in Table 1. The cumulative effect of the mutations in each isolated polypeptide molecule *in vivo* is to produce

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an epilepsy or another disorder associated with ion channel dysfunction as described above in said mammal.

In a particularly preferred embodiment of the present invention, the isolated polypeptides have an amino acid sequence as shown in any one of SEQ ID Numbers: 73-95. The sequences correspond to the novel amino acid changes laid out in Table 1.

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According to still another aspect of the present invention there is provided an isolated polypeptide comprising the amino acid sequence set forth in any one of SEQ ID Numbers: 73-95.

According to still another aspect of the present invention there is provided a polypeptide consisting of the amino acid sequence set forth in any one of SEQ ID Numbers: 73-95.

According to still another aspect of the present invention there is provided a method of preparing a polypeptide, comprising the steps of:

- (1) culturing host cells transfected with an expression vector comprising a nucleic acid molecule as described above under conditions effective for polypeptide production; and
- (2) harvesting the mutant ion channel subunit.

The mutant ion channel subunit may be allowed to assemble with other subunits constituting the channel that are either wild-type or themselves mutant subunits, whereby the assembled ion channel is harvested.

According to still another aspect of the invention there is provided a polypeptide which is the product of the process described above.

Substantially purified protein or fragments thereof can then be used in further biochemical analyses to establish secondary and tertiary structure. Such methodology is known in the art and includes, but is not restricted to, X-ray crystallography of crystals of the proteins or of the assembled ion channel incorporating the proteins or by nuclear magnetic resonance (NMR).

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Determination of structure allows for the rational design of pharmaceuticals to interact with the ion channel as a whole or through interaction with a specific subunit protein (see drug screening below), alter the overall ion channel protein charge configuration or charge interaction with other proteins, or to alter its function in the cell.

It will be appreciated that the mutant ion channel subunits included as part of the present invention will be useful in further applications which include a variety of hybridisation and immunological assays to screen for and detect the presence of either a normal or mutated gene or gene product. The invention enables therapeutic methods for the treatment of epilepsy as well as other disorders associated with ion channel dysfunction and also enables methods for the diagnosis or prognosis of epilepsy as well as other disorders associated with ion channel dysfunction.

Therapeutic Applications

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According to still another aspect of the invention there is provided a method of treating epilepsy as well as other disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic migraine, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night colour-blindness, blindness ortotal comprising administering a selective antagonist, agonist or modulator of an ion channel or ion channel subunit, when the ion channel contains a mutation in a subunit comprising the channel, as described above, to a subject in need of such treatment. Said mutation event may be causative of the

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disorder when expressed alone or when expressed in combination with one or more additional mutations in subunits of the same or different ion channels, which are typically those identified in Table 1.

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In still another aspect of the invention there is provided the use of a selective antagonist, agonist or modulator of an ion channel or ion channel subunit when ion channel contains a mutation in a comprising the channel, as described above, said mutation being causative of epilepsy as well as other disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, arrhythmias, episodic ataxia, migraine, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatorychronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness, when expressed alone or when expressed in combination with a second mutation in a subunit of the same or different ion channel, as described above, in the manufacture of a medicament for the treatment of the disorder.

In one aspect, a suitable antagonist, agonist or modulator will restore wild-type function to the ion channel or channels containing the mutations of the present invention, or will negate the effects the mutant channel or channels have on cell function.

Using methods well known in the art, a mutant ion channel may be used to produce antibodies specific for the mutant channel that is causative of the disease or to screen libraries of pharmaceutical agents to identify those that bind the mutant ion channel.

In one aspect, an antibody, which specifically binds to a mutant ion channel or mutant ion channel subunit of

invention, may be used directly as an

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antagonist or modulator, or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues that express the mutant ion channel.

In a still further aspect of the invention there is provided an antibody which is immunologically reactive with a polypeptide as described above, but not with a wild-type ion channel or ion channel subunit thereof.

In particular, there is provided an antibody to an assembled ion channel containing a mutation in a subunit comprising the channel, which is causative of epilepsy or another disorder associated with ion channel dysfunction when expressed alone or when expressed in combination with one or more other mutations in subunits of the same or different ion channels. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies as would be understood by the person skilled in the art.

For the production of antibodies, various hosts including rabbits, rats, goats, mice, humans, and others may be immunized by injection with a polypeptide as described above or with any fragment or oligopeptide. thereof which has immunogenic properties. adjuvants may be used to increase immunological response and include, but are not limited to, Freund's, mineral gels such as aluminium hydroxide, and surface-active substances such as lysolecithin. Adjuvants used in humans include BCG (bacilli Calmette-Guerin) and Corynebacterium parvum.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to the mutant ion channel have an amino acid sequence consisting of at least 5 amino acids, and, more preferably, of at least 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring

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molecule. Short stretches of ion channel amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to a mutant ion channel may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (For example, see Kohler et al., 1975; Kozbor et al., 1985; Cote et al., 1983; Cole et al., 1984).

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Monoclonal antibodies produced may include, but are not limited to, mouse-derived antibodies, humanised antibodies and fully human antibodies.

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (For example, see Orlandi et al., 1989; Winter and Milstein, 1991).

Antibody fragments which contain specific binding sites for a mutant ion channel may also be generated. For example, such fragments include, F(ab')2 fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (For example, see Huse et al., 1989).

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding immunoradiometric assays using either polyclonal monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between channel and its specific antibody. A two-site, monoclonalWO 2005/014863 PCT/AU2004/001051
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based immunoassay utilizing antibodies reactive to two non-interfering ion channel epitopes is preferred, but a competitive binding assay may also be employed.

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a further aspect of the invention there provided a method of treating epilepsy as well as other disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic migraine, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night total colour-blindness, blindness or comprising administering an isolated nucleic acid molecule which is the complement (antisense) of any one of the nucleic acid molecules described above and which encodes molecule that hybridizes with the mRNA encoding a mutant ion channel subunit of the invention, to a subject in need of such treatment.

In a still further aspect of the invention there is provided the use of an isolated nucleic acid molecule which is the complement (antisense) of a nucleic acid molecule of the invention and which encodes an molecule that hybridizes with the mRNA encoding a mutant ion channel subunit of the invention, in the manufacture of a medicament for the treatment of epilepsy as well as other disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic ataxia, migraine, Alzheimer's disease, Parkinson's schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney

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disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness.

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Typically, a vector expressing the complement (antisense) of the polynucleotides of the invention may be administered to a subject in need of such treatment. Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (For example, see Goldman et al., 1997).

Additional antisense or gene-targeted silencing strategies may include, but are not limited to, the use of antisense oligonucleotides, injection of antisense RNA, transfection of antisense RNA expression vectors, and the use of RNA interference (RNAi) or short interfering RNAs (siRNA). Still further, catalytic nucleic acid molecules such as DNAzymes and ribozymes may be used for gene silencing (Breaker and Joyce, 1994; Haseloff and Gerlach, 1988). These molecules function by cleaving their target mRNA molecule rather than merely binding to it as in traditional antisense approaches.

In a further aspect, a suitable agonist, antagonist or modulator may include peptides, phosphopeptides or small organic or inorganic compounds that can restore wild-type activity of ion channels containing mutations in the subunits which comprise the channels as described above.

Peptides, phosphopeptides or small organic or inorganic compounds suitable for therapeutic applications may be identified using nucleic acids and peptides of the invention in drug screening applications as described below. Molecules identified from these screens may also be

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of therapeutic application in affected individuals carrying other ion channel subunit gene mutations if the molecule is able to correct the common underlying functional deficit imposed by these mutations and those of the invention.

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There is therefore provided a method of treating epilepsy as well as other disorders associated with ion channel dysfunction comprising administering a compound that is a suitable agonist, antagonist or modulator of an ion channel and that has been identified using the mutant ion channel subunits of the invention.

instances, an appropriate approach some treatment may be combination therapy. This may involve the administering an antibody or complement (antisense) to a mutant ion channel or ion channel subunit of the invention inhibit its functional effect, combined administration of wild-type ion channel subunits which may restore levels of wild-type ion channel formation to normal levels. Wild-type ion channel subunits of the invention can be administered using gene therapy approaches as described above for complement administration.

There is therefore provided a method of treating epilepsy as well as other disorders associated with ion channel dysfunction comprising administration of an antibody or complement to a mutant ion channel or ion channel subunit of the invention in combination with administration of wild-type ion channel subunits.

In still another aspect of the invention there is provided the use of an antibody or complement to a mutant ion channel or ion channel subunit of the invention in combination with the use of wild-type ion channel subunits, in the manufacture of a medicament for the treatment of epilepsy as well as other disorders associated with ion channel dysfunction.

In further embodiments, any of the agonists, antagonists, modulators, antibodies, complementary

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sequences or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents may be made by those skilled inthe art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, therapeutic efficacy with lower dosages of each agent may be possible, thus reducing the potential for adverse side effects.

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

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Drug Screening

According to still another aspect of the invention, nucleic acid molecules of the invention as well peptides of the invention, particularly purified mutant ion channel subunit polypeptide and cells expressing these, are useful for the screening of candidate pharmaceutical agents for the treatment of epilepsy as well as other as other disorders associated with ion channel dysfunction, including but not restricted to, hypo-kalemic periodic paralysis, hyper- or myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, ataxia, migraine, Alzheimer's episodic schizophrenia, hyperekplexia, Parkinson's disease, depression, phobic obsessive anxiety, symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness.

35 Still further, it provides the use of a polypeptide complex for the screening of candidate pharmaceutical compounds.

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Still further, it provides the use wherein high throughput screening techniques are employed.

Compounds that can be screened in accordance with the invention include, but are not limited to peptides (such as soluble peptides), phosphopeptides and small organic or inorganic molecules (such as natural product or synthetic chemical libraries and peptidomimetics).

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In one embodiment, a screening assay may include a cell-based assay utilising eukaryotic or prokaryotic host cells that are stably transformed with recombinant molecules expressing the polypeptides or fragments of the invention, in competitive binding assays. Binding assays will measure the formation of complexes between a specific mutant ion channel subunit polypeptide or ion channel incorporating a mutant ion channel subunit polypeptide, and the compound being tested, or will measure the degree to which a compound being tested will inhibit or restore the formation of a complex between a specific mutant ion channel subunit polypeptide or ion channel incorporating a mutant ion channel subunit polypeptide, and its interactor or ligand.

The invention is particularly useful for screening compounds by using the polypeptides of the invention in transformed cells, transfected or injected oocytes, or animal models bearing mutated ion channel subunits such as transgenic animals or gene targeted (knock-in) animals (see transformed hosts). Drug candidates can be added to cultured cells that express a single mutant ion channel subunit or combination of mutant ion channel subunits (appropriate wild-type ion channel subunits should also be expressed for receptor assembly), can be added to oocytes transfected or injected with either a mutant ion channel subunit or combination of mutant ion channel subunits (appropriate wild-type ion channel subunits must also be injected for receptor assembly), or can be administered to animal model containing a mutant ion channel combination of mutant ion channels. Determining the

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ability of the test compound to modulate mutant ion channel activity can be accomplished by a number of techniques known in the art. These include for example measuring the effect on the current of the channel (e.g. calcium-, chloride-, sodium-, potassium-ion flux) as compared to the current of a cell or animal containing wild-type ion channels. Current in cells can be measured by a number of approaches including the patch-clamp technique (methods described in Hamill et al, 1981) or using fluorescence based assays as are known in the art (see Gonzalez et al. 1999). Drug candidates that alter the current to a more normal level are useful for treating or preventing epilepsy as well as other disorders associated with ion channel dysfunction.

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cell-based may also Non assays be used for identifying compounds that can inhibit or restore binding between the polypeptides of the invention or ion channels incorporating the polypeptides of the invention, and their interactors. Such assays are known in the art and include example AlphaScreen technology (PerkinElmer Sciences, MA, USA). This application relies on the use of beads such that each interaction partner is bound to a separate bead via an antibody. Interaction of each partner will bring the beads into proximity, such that laser excitation initiates a number of chemical leading to fluorophores emitting a ultimately signal. Candidate compounds that inhibit the binding of mutant ion channel subunit, or ion channel incorporating the mutant subunit, with its interactor will result loss ο£ light emission, while in candidate compounds that restore the binding of the mutant ion channel subunit, or ion channel incorporating the mutant subunit, with its interactor will result in positive light emission. These assays ultimately enable identification and isolation of the candidate compounds.

High-throughput drug screening techniques may also employ methods as described in WO84/03564. Small peptide

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test compounds synthesised on a solid substrate can be assayed for mutant ion channel subunit polypeptide or mutant ion channel binding. Bound mutant ion channel or mutant ion channel subunit polypeptide is then detected by methods well known in the art. In a variation of this technique, purified polypeptides of the invention can be coated directly onto plates to identify interacting test compounds.

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The invention also contemplates the use of competition drug screening assays in which neutralizing antibodies capable of specifically binding the mutant ion channel compete with a test compound for binding thereto. In this manner, the antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants of the mutant ion channel.

The polypeptides of the present invention may also be used for screening compounds developed as a result of combinatorial library technology. This provides a way to test a large number of different substances for their ability to modulate activity of a polypeptide. A substance identified as a modulator of polypeptide function may be peptide or non-peptide in nature. Non-peptide molecules" are often preferred for many inpharmaceutical applications. In addition, a mimic or mimetic the substance may $\circ f$ be designed for pharmaceutical use. The design of mimetics based on a known pharmaceutically active compound ("lead" compound) common approach to the development of pharmaceuticals. This is often desirable where the original active compound is difficult or expensive to synthesise or where it provides an unsuitable method of administration. In the design of a mimetic, particular parts of the original active compound that are important in determining the target property are identified. These parts or residues constituting the active region of the compound are known as its pharmacophore. Once found, pharmacophore structure is modelled according to its

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physical properties using data from a range of sources including x-ray diffraction data and NMR. A template molecule is then selected onto which chemical groups which mimic the pharmacophore can be added. The selection can be made such that the mimetic is easy to synthesise, is likely to be pharmacologically acceptable, does not degrade in vivo and retains the biological activity of the lead compound. Further optimisation or modification can be carried out to select one or more final mimetics useful for in vivo or clinical testing.

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It is also possible to isolate a target-specific antibody and then solve its crystal structure. principle, this approach yields a pharmacophore upon which subsequent drug design can be based as described above. It may be possible to avoid protein crystallography altogether by generating anti-idiotypic antibodies (antiids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analogue of the original receptor. The anti-id could then be used to isolate peptides from chemically or biologically produced peptide banks.

Another alternative method for drug screening relies on structure-based rational drug design. Determination of the three dimensional structure of the polypeptides of the invention, or the three dimensional structure of the ion channels which incorporate these polypeptides allows for structure-based drug design to identify biologically active lead compounds.

Three dimensional structural models can be generated by a number of applications, some of which include experimental models such as x-ray crystallography and NMR and/or from in silico studies of structural databases such as the Protein Databank (PDB). In addition, three dimensional structural models can be determined using a number of known protein structure prediction techniques based on the primary sequences of the polypeptides (e.g.

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SYBYL - Tripos Associated, St. Louis, MO), de novo protein structure design programs (e.g. MODELER - MSI Inc., San Diego, CA, or MOE - Chemical Computing Group, Montreal, Canada) or ab initio methods (e.g. see US Patent Numbers 5331573 and 5579250).

Once the three dimensional structure of a polypeptide or polypeptide complex has been determined, structurebased drug discovery techniques can be employed to design biologically-active compounds based on these dimensional structures. Such techniques are known in the art and include examples such as DOCK (University of California, San Francisco) or AUTODOCK (Scripps Research Institute, La Jolla, California). A computational docking protocol will identify the active site or sites that are deemed important for protein activity based on a predicted protein model. Molecular databases, such as the Available Chemicals Directory (ACD) are then screened for molecules that complement the protein model.

Using methods such as these, potential clinical drug candidates can be identified and computationally ranked in order to reduce the time and expense associated with typical 'wet lab' drug screening methodologies.

Compounds identified through screening procedures as described above, and which are based on the use of the mutant nucleic acid and polypeptides of the invention, can also be tested for their effect on correcting the functional deficit imposed by other gene mutations in affected individuals including other ion channel subunit mutations.

Such compounds form a part of the present invention, as do pharmaceutical compositions containing these and a pharmaceutically acceptable carrier.

Pharmaceutical Preparations

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Compounds identified from screening assays and shown to restore ion channel wild-type activity can be administered to a patient at a therapeutically effective

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dose to treat or ameliorate epilepsy as well as other disorders associated with ion channel dysfunction, described above. A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms of the disorder.

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Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals. The data obtained from these studies can then be used in the formulation of a range of dosages for use in humans.

Pharmaceutical compositions for use in accordance with the present invention can be formulated conventional manner using one or more physiological acceptable carriers, excipients or stabilisers which are well known. Acceptable carriers, excipients or stabilizers are non-toxic at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including absorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; binding agents including hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glutamine, asparagine, arginine glycine, monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or non-ionic surfactants such Tween, Pluronics or as polyethylene glycol (PEG).

The formulation of pharmaceutical compositions use in accordance with the present invention will be based proposed route of administration. Routes administration may include, but are not limited to, inhalation, insufflation (either through the mouth or nose), oral, buccal, rectal or parental administration. 35

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Diagnostic and Prognostic Applications

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Polynucleotide sequences encoding an ion channel subunit may be used for the diagnosis or prognosis of epilepsy, as well as other as other disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, ataxia, migraine, episodic Alzheimer's Parkinson's disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness, and the use of the nucleic molecules incorporated as part of the invention diagnosis orprognosis of these disorders, predisposition to these disorders, is therefore contemplated. The nucleic acid molecules incorporating the novel mutation events laid out in Table 1 may be used for this purpose.

The polynucleotides that may be used for diagnostic or prognostic purposes include oligonucleotide sequences, genomic DNA and complementary RNA and DNA molecules. The polynucleotides may be used to detect and quantitate gene expression in biological samples. Genomic DNA used for the diagnosis or prognosis may be obtained from body cells, such as those present in the blood, tissue biopsy, surgical specimen, or autopsy material. The DNA may be isolated and used directly for detection of a specific sequence or may be amplified by the polymerase chain reaction (PCR) prior to analysis. Similarly, RNA or cDNA may also be used, with or without PCR amplification. To detect a specific nucleic acid sequence, hybridisation using specific oligonucleotides, restriction enzyme digest and mapping, PCR mapping, RNAse protection, and various other methods may be employed. Oligonucleotides specific

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to particular sequences can be chemically synthesized and labelled radioactively or nonradioactively and hybridised to individual samples immobilized on membranes or other solid-supports or in solution. The presence, absence or excess expression of any one of the mutant ion channel genes of the invention may then be visualized using methods such as autoradiography, fluorometry, or colorimetry.

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In a further diagnostic or prognostic approach, the nucleotide sequences of the invention may be useful in assays that detect the presence of associated disorders, particularly those mentioned previously. The nucleotide sequences may be labelled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridisation complexes. After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis or prognosis of epilepsy and other disorders as described above, which are associated with the ion channel subunit mutations or variants of the invention, the nucleotide sequence of each gene can be compared between normal tissue and diseased tissue in order to establish whether the patient expresses a mutant gene.

In order to provide a basis for the diagnosis or of prognosis a disorder associated with of an expression ion channel subunit of gene invention, a normal or standard profile for expression is established. This may be accomplished by combining body WO 2005/014863 PCT/AU2004/001051
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fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding the relevant ion channel subunit gene, under conditions suitable for hybridisation or amplification. Standard hybridisation may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Another method identify a normal or standard profile for expression of an ion channel subunit gene is through quantitative RT-PCR RNA isolated from body cells of studies. individual is reverse transcribed and real-time PCR using specific for the oligonucleotides relevant conducted to establish a normal level of expression of the gene. Standard values obtained in both these examples may be compared with values obtained fromsamples patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

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Once the presence of a disorder is established and a treatment protocol is initiated, hybridisation assays or quantitative RT-PCR studies may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

According to a further aspect of the invention there is provided the use of a polypeptide as described above in the diagnosis or prognosis of epilepsy as well as other disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic Alzheimer's disease, Parkinson's migraine, disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain,

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chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness.

When a diagnostic or prognostic assay is to be based upon proteins constituting an ion channel, a variety of approaches are possible. For example, diagnosis prognosis can be achieved by monitoring differences in the electrophoretic mobility of normal and mutant proteins that form the ion channel. Such an approach will be particularly useful in identifying mutants in which charge substitutions are present, orwhich ininsertions, deletions or substitutions have resulted in a significant change in the electrophoretic migration of the resultant protein. Alternatively, diagnosis or prognosis may be based upon differences in the proteolytic cleavage patterns of normal and mutant proteins, differences molar ratios of the various amino acid residues, or by functional assays demonstrating altered function of the gene products.

In another aspect, antibodies that specifically bind mutant ion channels may be used for the diagnosis or prognosis of a disorder, or in assays to monitor patients being treated with a complete ion channel or agonists, antagonists, modulators or inhibitors of an ion channel. Antibodies useful for diagnostic or prognostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic or prognostic assays for ion channels include methods that utilize the antibody and a label to detect a mutant ion channel in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labelled by or non-covalent attachment of covalent a reporter molecule.

A variety of protocols for measuring the presence of mutant ion channels, including but not restricted to, ELISAs, RIAs, and FACS, are known in the art and provide a

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for diagnosing or prognosing a disorder. The expression of a mutant ion channel or combination of mutant ion channels is established by combining body or cell extracts fluids taken fromtest mammalian subjects, preferably human, with antibody to the channel or channels under conditions suitable for complex of formation. The amount complex formation quantitated by various methods, preferably by photometric means. Antibodies specific for the mutant ion channels will only bind to individuals expressing the said mutant ion channels and not to individuals expressing only wildtype channels (ie normal individuals). This establishes the basis for diagnosing the disorder.

Once an individual has been diagnosed or prognosed with a disorder, effective treatments can be initiated as described above. Treatments can be directed to amend the combination of ion channel subunit mutations or may be directed to one mutation.

20 Microarray

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In further embodiments, complete cDNAs, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as probes in a microarray. The microarray can be used to diagnose or prognose epilepsy, as well as other disorders associated with ion channel dysfunction, through identification of genetic variants, mutations, polymorphisms in the ion channel subunits that form part of the invention, to understand the genetic basis of a or can be used to develop and monitor activities of therapeutic agents.

According to a further aspect of the present invention, tissue material obtained from genetically modified non-human animal models generated as a result of the identification of specific ion channel subunit human mutations (see below), particularly those disclosed in the present invention, can be used in microarray experiments.

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These experiments can be conducted to identify the level of expression of specific ion channel subunits, or the level of expression of any cDNA clone from whole-tissue libraries, in diseased tissue as opposed to normal control tissue. Variations in the expression level of genes, including ion channel subunits, between the two tissues indicates their possible involvement in the process either as a cause or consequence of the original ion channel subunit mutation present in the animal model. These experiments may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose or prognose a disorder, and to develop and monitor the activities of therapeutic agents. Microarrays may be prepared, used, and analyzed using methods known in the art. (For example, see Schena et al., 1996; Heller et al., 1997).

Transformed Hosts

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present invention also provides The for production of genetically modified (knock-out, knock-in and transgenic), non-human animal models comprising nucleic acid molecules containing the novel ion channel mutations or variants as laid out in Table 1. These animals are useful for the study of the function of ion channels, to study the mechanisms by which combinations of mutations in ion channel subunits interact to give rise to disease and the effects of these mutations on tissue development, for the screening of candidate pharmaceutical compounds, for the creation of explanted mammalian cell cultures which express mutant ion channels or combinations of mutant ion channels, and for the evaluation of potential therapeutic interventions.

Animal species which are suitable for use in the animal models of the present invention include, but are not limited to, rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs, and non-human primates such as monkeys and chimpanzees. For initial

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studies, genetically modified mice and rats are highly desirable due to the relative ease in generating knock-in, knock-out or transgenics of these animals, their ease of maintenance and their shorter life spans. For certain studies, transgenic yeast or invertebrates may be suitable and preferred because they allow for rapid screening and provide for much easier handling. For longer term studies, non-human primates may be desired due to their similarity with humans.

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To create an animal model for a mutated ion channel, animal model incorporating a combination mutations, several methods can be employed. These include, but are not limited to, generation of a specific mutation in a homologous animal gene, insertion of a wild type human gene and/or a humanized animal gene by homologous recombination, insertion of a mutant (single or multiple) human gene as genomic or minigene cDNA constructs using wild type or mutant or artificial promoter elements, or insertion of artificially modified fragments the gene by homologous recombination. The endogenous modifications include insertion of mutant stop codons, the of DNA sequences, the inclusion of deletion orrecombination elements (lox p sites) recognized by enzymes such as Cre recombinase.

To create transgenic mice in order to study gain of gene function in vivo, any mutant ion channel subunit gene of the invention can be inserted into a mouse germ line using standard techniques such as oocyte microinjection. Gain of gene function can mean the over-expression of a its protein product, orthe gene and of a mutation o£ complementation the gene under investigation. For occyte injection, one or more copies of the mutant gene can be inserted into the pronucleus of a oocyte. This oocyte just-fertilized mouse is into a pseudo-pregnant foster mother. The reimplanted live-born mice can then be screened for integrants using analysis of tail DNA for the presence of the relevant

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human ion channel subunit gene sequence. The transgene can be either a complete genomic sequence injected as a YAC, BAC, PAC or other chromosome DNA fragment, a cDNA with either the natural promoter or a heterologous promoter, or a minigene containing all of the coding region and other elements found to be necessary for optimum expression.

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To generate knock-out mice or knock-in mice, gene targeting through homologous recombination in mouse embryonic stem (ES) cells may be applied. Knock-out mice are generated to study loss of gene function in vivo while knock-in mice (which are preferred) allow the study of gain of function or to study the effect of specific gene mutations. Knock-in mice are similar to transgenic mice however the integration site and copy number are defined in the former.

For knock-out mouse generation, gene targeting vectors can be designed such that they delete (knock-out) the protein coding sequence of the relevant ion channel subunit gene in the mouse genome. In contrast, knock-in mice can be produced whereby a gene targeting vector containing the relevant ion channel subunit gene can integrate into a defined genetic locus in the mouse genome. For both applications, homologous recombination is catalysed by specific DNA repair enzymes that recognise homologous DNA sequences and exchange them via double crossover.

Gene targeting vectors are usually introduced into ES cells using electroporation. ES cell integrants are then isolated via an antibiotic resistance gene present on the targeting vector and are subsequently genotyped to identify those ES cell clones in which the gene under investigation has integrated into the locus of interest. The appropriate ES cells are then transmitted through the germline to produce a novel mouse strain.

In instances where gene ablation results in early embryonic lethality, conditional gene targeting may be employed. This allows genes to be deleted in a temporally

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and spatially controlled fashion. As above, appropriate ES cells are transmitted through the germline to produce a novel mouse strain, however the actual deletion of the gene is performed in the adult mouse in a tissue specific or time controlled manner. Conditional gene targeting is most commonly achieved by use of the cre/lox system. The enzyme cre is able to recognise the 34 base pair loxP sequence such that loxP flanked (or floxed) recognised and excised by cre. Tissue specific cre expression in transgenic mice enables the generation of tissue specific knock-out mice by mating gene targeted floxed mice with cre transgenic mice. Knock-out can be conducted in every tissue (Schwenk et al., 1995) using the 'deleter' mouse or using transgenic mice with an inducible cre gene (such as those with tetracycline inducible cre genes), or knock-out can be tissue specific for example through the use of the CD19-cre mouse (Rickert et al., 1997).

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Once knock-in animals have been produced contain a specific mutation in a particular ion channel subunit, mating combinations may be initiated between such animals so as to produce progeny containing combinations two or more ion channel mutations. effectively mimic combinations of mutations that proposed to cause human IGE cases. These animal models can subsequently be used to study the extent and mechanisms of the mutated as related to ion channel disease combinations, as well as for the screening of candidate therapeutic compounds.

According to still another aspect of the invention there is provided the use of genetically modified non-human animals as described above for the screening of candidate pharmaceutical compounds (see drug screening above). These animals are also useful for the evaluation (eg therapeutic efficacy, toxicity, metabolism) of candidate pharmaceutical compounds, including those identified from the invention as described above, for the

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treatment of epilepsy as well as other as other disorders associated with ion channel dysfunction as described above.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.

Throughout this specification and the claims, the words "comprise", "comprises" and "comprising" are used in a non-exclusive sense, except where the context requires otherwise.

It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding, various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification.

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Brief Description of the Drawings

Preferred forms of the invention will now be described, by way of example only, with reference to the following examples and the accompanying drawings, in which:

Figure 1 provides an example of ion channel subunit stoichiometry and the effect of multiple versus single ion channel subunit mutations. Figure 1A: A typical channel may have five subunits of three different types. Figure 1B: In outbred populations complex diseases such as idiopathic generalized epilepsies may be due to mutations in two (or more) different subunit genes. Because only one allele of each subunit gene is abnormal, half the expressed subunits will have the mutation. Figure 1C: In inbred populations, both alleles of a single subunit gene will be affected, so all expressed subunits will be mutated. Figure 1D: Autosomal dominant disorders can be

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attributed to single ion channel subunit mutations that give rise to severe functional consequences.

Figure 2 represents the location of mutations identified in the KCNQ2 ion channel subunit constituting the potassium channel. M: Missense mutation; T: Truncation mutation; F: Frameshift mutation; S: Splice site mutation.

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Figure 3 provides examples of epilepsy pedigrees where mutation profiles of ion channel subunits for individuals constituting the pedigree have begun to be determined. These examples have been used to illustrate how the identification of novel ion channel subunit mutations and variations in IGE individuals can combine to give rise to the disorder.

4 shows the results of yeast two-hybrid Figure analysis of R353G and L619R KCNQ2 mutants. Yeast were transformed with the empty DB (BAIT) plasmid (DBLeu), DB-Q2C wt, DB-Q2C R353G mutant or the DB-Q2 L619R mutant as indicated in A and the AD-CaM (TARGET) vector was qap-repair. introduced by Yeast control (InvitrogenTM) were included on all plates for comparison. Control 1 has no interaction. Control 2 has a weak 3 interaction. Control has moderately a interaction. Control 4 has a strong interaction control 5 has a very strong interaction. B. Growth of transformed yeast and controls on -leu -tryp selection. Yeast can grow on -leu if they contain the DB plasmid, and -tryp if they have AD plasmid. C. Growth of transformed yeast and controls on -leu -tryp -his +40mM 3AT after 48hrs. Yeast can grow on -his+3AT if the his reporter gene is activated by interaction between the BAIT and TARGET plasmids. D-F. LacZ Filter assay for interaction between BAIT and TARGET plasmids, photos taken after 2hrs (D), 7hrs (E) and 24hrs (F). Activation of the β -galactosidase reporter gene by interaction of the BAIT and TARGET plasmids leads to the dark appearance of colonies.

Figure 5 shows the results of CaM affinity experiments with the R353G and L619R KCNQ2 mutants. The

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chart below shows the values from the CPRG assay for β -galactosidase activity as a measure of KCNQ2C-CaM binding efficiency. The area of each bar in the chart equates to the CaM binding efficiency of the BAIT. Broken lines indicate statistical comparison by Student's t test * P<0.01, ** P<0.001.

Modes for Performing the Invention

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Potassium channels are the most diverse class of ion channel. The *C. elegans* genome encodes about 80 different potassium channel genes and there are probably more in mammals. About ten potassium channel genes are known to be mutated in human disease and include four members of the KCNQ gene sub-family of potassium channels. KCNQ proteins have six transmembrane domains, a single P-loop that forms the selectivity filter of the pore, a positively charged fourth transmembrane domain that probably acts as a voltage sensor, and intracellular amino and carboxy termini. The C-terminus is long and contains a conserved "A domain" followed by a short stretch thought to be involved in subunit assembly.

Four KCNQ subunits are thought to combine to form a functional potassium channel. All five known KCNQ proteins can form homomeric channels in vitro and the formation of heteromers appears to be restricted to combinations. For instance KCNQ2 and KCNQ3, which are predominantly expressed in the central nervous system, form a heteromultimeric channel that mediates the neuronal muscarinic-regulated current (M-current), also known as the M-channel (or M-type K+ channel). The M-current is a slowly activating, non-inactivating potassium conductance known to regulate neuronal excitability by determining the firing properties of neurons and their responsiveness to synaptic input (Wang et al., 1998). Because it is the only current active at voltages near the threshold for action potential initiation, the M-current has a major impact on neuronal excitability.

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Sodium (the alpha subunit) and calcium channels are thought to have evolved from the potassium channel subunit, and they each consist of four domains covalently linked as the one molecule, each domain being equivalent to one of the subunits that associate to form the potassium channel. Each of the four domains of the sodium and calcium channels are comprised of six transmembrane segments.

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Voltage-gated sodium channels are required generate the electrical excitation in neurones, heart and skeletal muscle fibres, which express tissue specific isoforms. Sodium channels are heteromers of a pore forming alpha subunit and a modulatory beta-1 subunit, with an additional beta-2 subunit in neuronal channels. Ten genes encoding sodium channel alpha subunits and 3 encoding different beta subunits have so far identified. The beta subunits of the sodium channels do. not associate with the alpha subunits to form any part of the pore, they do however affect the way the alpha pore forming subunit functions.

As with sodium channels, calcium channels consist of a single pore forming alpha subunit, of which at least six types have been identified to date, and several accessory subunits including four beta, one gamma and one alpha2-delta gene. Many of these subunits also encode multiple splice variants adding to the diversity of receptor subunits of this family of ion channels.

The ion channels in the nAChR/GABA super family show a theoretical pentameric channel. Gamma-Aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the central nervous system. GABA-ergic inhibition is mediated by two major classes of receptors, type A (GABA-A) and type B (GABA-B). GABA-B receptors are members of the class of receptors coupled to G-proteins and mediate a variety of inhibitory effects via secondary messenger cascades. GABA-A receptors are ligand-gated chloride channels that mediate rapid inhibition.

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The GABA-A channel has 16 separate, but related, genes encoding subunits. These are grouped on the basis of sequence identity into alpha, beta, gamma, delta, epsilon, theta and pi subunits. There are six alpha subunits (α 1- α 6), three beta subunits (β 1- β 3) and three gamma subunits (γ 1- γ 3). Each GABA-A receptor comprises five subunits which may, at least in theory, be selected from any of these subunits.

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Neuronal nicotinic acetylcholine receptors (nAChRs) consist of heterologous pentamers comprising various combinations of alpha subunits or alpha and beta subunits $(\alpha 2 - \alpha 9; \beta 2 - \beta 4)$. The alpha subunits are characterised by adjacent cysteine residues at amino acid positions 192 and 193, and the beta subunits by the lack of these cysteine residues. They are ligand-gated ion channels differentially expressed throughout the brain to physiologically and pharmacologically distinct receptors hypothesised to mediate fast, excitatory transmission between neurons of the central nervous system or to modulate neurotransmission fromtheir presynaptic position.

In chicken and rat, the predominant nAChR subtype is composed of alpha-4 and beta-2 subunits. The transmembrane 2 (M2) segments of the subunits are arranged as helices and contribute to the walls of neurotransmitter-gated ion channel. The alpha helices appear to be kinked and orientated in such a way that the side chains of the highly conserved M2-leucine residues project inwards when the channel is closed. ACh is thought cause a conformational change by altering association of the amino acid residues of M2. The opening of the channel seems to be due to rotations of the gate forming side chains of the amino acid residues; the conserved polar serines and threonines may form the critical gate in the open channel.

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Example 1: Identification of mutations in ion channels

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Previous studies by reference (Wallace et al., 1998; PCT/AU01/00581; Wallace et al., 2001b; Australian patent AU-B-56247/96; Steinlein et al., 1995; PCT/AU01/00541; Phillips et al., 2001; PCT/AU01/00729; PCT/AU01/01648; PCT/AU02/00910; Wallace et al., 2001a, the disclosures of incorporated herein by reference) identified mutations in a number of ion channel subunits associated with epilepsy. These include ion channel subunits of voltage-gated (eq SCN1A, SCN1B, KCNQ2, KCNQ3) or ligand-gated (eg CHRNA4, CHRNB2, GABRG2, GABRD) types. identify further mutations in ion channel subunits which comprise the ion channels were screened for molecular defects in epilepsy patients.

Human genomic sequence available from the Human Genome Project was used to characterize the genomic organisation for each subunit gene. Each subsequently screened for sequence changes using single strand conformation polymorphism (SSCP) analysis large sample of epileptics with common sporadic subtypes eg juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE) and epilepsy with generalized tonic-clonic seizures (TCS). Clinical observations can then be compared molecular defects characterized in order to establish the combinations of mutant subunits involved in the various disease states, and therefore to provide validated drug targets for each of these disease states. This will provide a basis for novel drug treatments directed at the genetic defects present in each patient.

The coding sequence for each of the ion channel subunits was aligned with human genomic sequence present in available databases at the National Centre for Biotechnology Information (NCBI). The BLASTN algorithm was typically used for sequence alignment and resulted in the genomic organisation (intron-exon structure) of each gene being determined. Where genomic sequence for an ion

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channel subunit was not available, BACs or PACs containing the relevant ion channel subunit were identified through screening of high density filters containing these clones and were subsequently sequenced.

Availability of entire genomic sequence for each ion channel subunit facilitated the design of intronic primers spanning each exon. These primers were used for both high throughput SSCP screening and direct DNA sequencing.

10 Example 2: Sample preparation for SSCP screening

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A large collection of individuals affected with epilepsy have undergone careful clinical phenotyping and additional data regarding their family history has been collated. Informed consent was obtained from each individual for blood collection and its use in subsequent experimental procedures. Clinical phenotypes incorporated classical IGE cases as well as GEFS+ and febrile seizure cases.

DNA was extracted from collected blood using the QIAamp DNA Blood Maxi kit (Qiagen) according to manufacturers specifications or through procedures adapted from Wyman and White (1980). Stock DNA samples were kept at a concentration of 1 ug/ul.

In preparation for SSCP analysis, samples to be screened were formatted into 96-well plates at a concentration of 30 ng/ul. These master plates were subsequently used to prepare exon specific PCR reactions in the 96-well format.

30 Example 3: Identification of sequence alterations in ion channel genes

SSCP analysis of specific ion channel exons followed by sequencing of SSCP bandshifts was performed on individuals constituting the 96-well plates to identify sequence alterations.

Primers used for SSCP were labelled at their 5' end with HEX and typical PCR reactions were performed in a

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total volume of 10 μ l. All PCR reactions contained 67 mM Tris-HCl (pH 8.8); 16.5 mM (NH₄)₂SO₄; 6.5 μ M EDTA; 1.5 mM MgCl₂; 200 μ M each dNTP; 10% DMSO; 0.17 mg/ml BSA; 10 mM β -mercaptoethanol; 5 μ g/ml each primer and 100 U/ml Taq DNA polymerase. PCR reactions were typically performed using 10 cycles of 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30 seconds followed by 25 cycles of 94°C for 30 seconds. A final extension reaction for 10 minutes at 72°C followed.

Ten to twenty μl of loading dye comprising 50% (v/v) formamide, 12.5 mM EDTA and 0.02% (w/v) bromophenol blue were added to completed reactions which were subsequently run on non-denaturing 4% polyacrylamide gels with a crosslinking ratio of 35:1 (acrylamide:bis-acrylamide) and containing 2% glycerol. Gel thickness was 100 μ m, width 168mm and length 160mm. Gels were run at 1200 volts and approximately 20mA, at 18°C and analysed on the GelScan 2000 system (Corbett Research, Australia) according to manufacturers specifications.

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PCR products showing a conformational change were sequenced. This subsequently first involved amplification of the amplicon from the relevant individual (primers used in this instance did not contain 5' labels) followed by purification of the PCR amplified templates for sequencing using QiaQuick PCR preps (Qiagen) based on manufacturers procedures. The primers used to sequence the purified amplicons were identical to those amplification step. the initial For for sequencing reaction, 25 ng of primer and 100 ng purified PCR template were used. The BigDye sequencing kit (ABI) was used for all sequencing reactions according to the manufacturers specifications. The products were run on an ABI 377 Sequencer and analysed using the EditView program.

Table 1 shows the novel sequence changes identified in the ion channel subunits screened.

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Example 4: Digenic model examples

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In some instances a single mutation in an ion channel alone is insufficient to give rise to an epilepsy phenotype. However combinations of mutations each conferring a subtle change of function to an ion channel, as proposed by the digenic model (PCT/AU01/00872), may be sufficient to produce an epilepsy phenotype.

mutations and variations ion insubunits previously identified, the digenic model may be validated through a parametric analysis of large families in which two abnormal alleles co-segregate by chance to identify mutations which act co-operatively to give an epilepsy phenotype. It is envisaged that the strategy of in these large careful clinical phenotyping together with a linkage analysis based on the digenic hypothesis will allow identification of the mutations in ion channels associated with IGEs. If molecular genetic successful using the studies in IGE are hypothesis, such an approach might serve as a model for other disorders with complex inheritance.

The digenic hypothesis predicts that the closer the genetic relationship between affected individuals, the more similar the sub-syndromes, consistent with published data (Italian League Against Epilepsy Genetic Collaborative Group, 1993). This is because more distant relatives are less likely to share the same combinations of mutated subunits.

Identical twins have the same pair of mutated subunits and the same minor alleles so the sub-syndromes are identical. Affected sib-pairs, including dizygous twins, with the same sub-syndrome would also have the same pair of mutated subunits, but differences in minor alleles would lead to less similarity than with monozygous twins. Some sib-pairs and dizygous twins, have quite different sub-syndromes; this would be due to different combinations of mutated subunits, when the parents have more than two mutated alleles between them.

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A special situation exists in inbred communities that parallels observations on autosomal recessive mouse models. Here the two mutated alleles of the digenic model are the same and thus result in a true autosomal recessive disorder. Because all affected individuals have the same pair of mutated alleles, and a similar genetic background, the phenotypes are very similar.

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In outbred communities approximately 1% of the population would have IGE genotypes (2 mutated alleles) and 0.3% would clinically express IGE. Most of these would have mutations in two different channel subunits. In such communities most cases would appear "sporadic" as the risk to first degree relatives would be less than 10%.

For example, let there be three IGE loci (A,B,C) and let the frequency of abnormal alleles (a*,b*,c*) at each locus be .027 and of normal alleles (a, b, c) be .973. Then, the distribution of genotypes aa*, a*a, a*a* and aa at locus A will be .0263 (.027 x .973), .0263, .0007 and .9467 respectively, and similarly for loci B and C. In this population .8485 will have no mutated alleles (.9467³), .1413 will have one mutated allele (a* or b* or c*; .0263 x .9467² x 6), .0098 will have two abnormal alleles (.0020 two same abnormal alleles, .0078, two different abnormal alleles) and 0.00037 will have more than two abnormal alleles. Thus in this population .01, or 1%, will have two or more abnormal alleles (IGE genotype), and the total abnormal allele frequency will be .08 (3 x .027).

To determine the familial risks and allele patterns in affected pairs, the frequency distribution of population matings and the percentage of children with 2 or more abnormal alleles must be determined. The frequency of matings with no abnormal alleles (0 \times 0) is .72 (.8485 2), for 1 \times 0 and 0 \times 1 matings .24 (2 \times .8485 \times .1413), for a 1 \times 1 mating .020, and for 2 \times 0 and 0 \times 2 matings .0166 etc. From this distribution of matings the frequency of children with 2 or more abnormal alleles can

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be shown to be .01. For example, the 0 x 2 and 2 x 0 matings contribute .0033 of this .01 frequency (.0166 [mating frequency] x .2 [chance of that mating producing a child with 2 or more abnormal alleles]).

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To determine parental risk it can be shown that of children with 2 abnormal alleles (IGE genotype), .49 derive from 1 x 1 matings where no parent is affected, .33 derive from a 2 x 0 and 0 x 2 matings etc. For the 2 x 0 and 0 x 2 matings, half the parents have IGE genotypes and contribute .16 (.33/2) to the parental risk with the total parental risk of an IGE genotype being .258. The other matings that contribute to affected parent-child pairs are 2×1 , 1×2 , 3×0 , 0×3 etc.

The sibling risk of an IGE genotype is .305. For example 2 x 0 and 0 x 2 matings contributed .08 to the sibling risk (.33[fraction of children with 2 abnormal alleles] x .25[the chance of that mating producing a child with 2 or more abnormal alleles]). Similarly the offspring risk was determined to be .248 by mating individuals with 2 abnormal alleles with the general population. Thus at 30% penetrance the risk for IGE phenotype for parents of a proband is .077, for siblings .091, and for offspring .074.

It can be shown that affected sib pairs share the same abnormal allele pair in 85% of cases. This is because of all affected sib pairs 44% derive from 1 x 1 matings and 23% from 0 x 2 and 2 x 0 matings where all affected siblings have the same genotype. In contrast, 24% derive from 1 x 2 matings and 9% from 3 x 1 and 2 x 2 matings etc where affected sibling genotypes sometimes differ.

For affected parent-child pairs, genotypes are identical in only 58%. Of affected parent child pairs, 43% derive from 0×2 matings where gentoypes are identical, whereas 38% derive from 0×3 and 17% from 1×2 where the majority of crosses yield different affected genotypes.

Based on the digenic model it has been postulated that most classical ${\sf IGE}$ and ${\sf GEFS}^+$ cases are due to the

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combination of two mutations in multi-subunit ion channels. These are typically point mutations resulting in a subtle change of function. The critical postulate is that two mutations, usually, but not exclusively, in different subunit alleles ("digenic model"), are required for clinical expression of IGE.

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The hypothesis that similar phenotypes can be caused by the combination of mutations in two (or more) different subunits (outbred communities), or by the same mutation in two (or more) alleles of the same subunit (inbred communities), may seem implausible. However, applying the digenic hypothesis to the theoretical pentameric channel shown in Figure 1, in outbred communities IGE will be due to subunit combinations such as $\alpha*\alpha\beta*\beta\Delta$, $\alpha*\alpha\beta\beta\Delta*$ or $\alpha\alpha\beta*\beta\Delta*$ (mutated subunits indicated by *). In inbred communities $\alpha*\alpha*\beta\beta\Delta$ or $\alpha\alpha\beta*\beta*\Delta$ combinations might cause IGE phenotypes. We assume that the mutations will not cause reduced expression of the alleles and that the altered ion channel excitability, and consequent IGE phenotype, caused by mutations in two different alleles is similar to that caused by the same mutation in both alleles of one subunit. Finally, subunit mutations with more severe functional consequences (eg breaking a disulphide bridge in SCN1B or amino acid substitution in the pore forming regions of SCN1A for GEFS+) cause autosomal dominant generalized epilepsies with a penetrance of 60-90%. Such "severe" mutations are rare (allele frequency <0.01%) and are infrequent causes of GEFS⁺. They very rarely, perhaps never, cause classical IGE.

The relative separate segregation of classical IGE and GEFS⁺ phenotypes is an anecdotal clinical observation of ours (Singh et al., 1999), although the separation is not absolute. The separation is supported by previous family and EEG studies of Doose and colleagues who described "type A" and "type B" liabilities which we may approximate the GEFS⁺ and classical IGE groupings respectively (Doose and Baier, 1987).

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The digenic model predicts that affected sib pairs will share the same genes in 85% of cases whereas they will have at least one different allele in the remaining 15%. In contrast, only 58% of parent-child pairs share the same alleles in a 3 locus model. Thus there should be greater similarity of syndromes between sibling pairs than parent-child pairs. This would be most objectively measured by age of onset and seizure types.

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Estimates for the risk of febrile seizures or IGE in The estimates range from 5%-10% relatives vary. siblings, 4%-6% for offspring, 3%-6% for parents, and 2-3% for grandparents. Underestimation may occur because IGE youth, and parents and particularly manifest ingrandparents may be unaware of seizures in themselves in younger years. This is particularly true where there was stigma associated with epilepsy and where the epilepsy may mild and unrecognized. Underestimation sibling and offspring risks occurs when unaffected young children are counted, some of whom will develop IGE in adolescence. Overestimation may occur with misdiagnosis of seizures or inclusion of seizures unrelated to IGE (e.g. due to trauma or tumors)

In autosomal dominant models the risk to affected relatives reduces proportionally (50% for first degree relatives, 25% for second degree etc). For all oligogenic or polygenic models the risk decreases more quickly. For a digenic model with three loci, the risks are 9.1% for siblings, 7.4% for offspring, 7.7% for parents. Rigorous measurement of the familial recurrence rates, with careful phenotyping and age-corrected risk estimates could be compared with the predictions from the digenic model, and it is proposed to do this.

There is a small amount of information on IGE families regarding haplotype distribution. For example, there is some evidence for a locus on 8q as determined by parametric linkage in a single family (Fong et al., 1998) and by non-parametric analysis in multiple small families

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(Zara et al., 1995). Interestingly, in the latter study the 8q haplotype not infrequently came from the unaffected parent. This would be quite compatible with the digenic model and evaluation of other data sets in this manner could be used to test the hypothesis, and it is proposed to do this.

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Following the analysis of one large family with epilepsy where the two main phenotypes were childhood absence epilepsy (CAE) and febrile seizures (FS), the inheritance of FS was found to be autosomal dominant and the penetrance 75%. However the inheritance of CAE in this family was not simple Mendelian, but suggestive of complex inheritance with the involvement of more than one gene. The power of this large family was used to explore the complex genetics of CAE further.

Linkage analysis on this family in which individuals with CAE, FS and FS+ were deemed affected led to the detection of linkage on chromosome 5q and identification of a mutation in the GABRG2 gene (R43Q) which is localised to this region (Wallace et al., 2001a; PCT/AU01/00729). All 10 tested individuals with FS alone in this family had this mutation and 7 CAE affected individuals in this family also had the mutation. To test the digenic model of IGEs in the CAE affected individuals, the whole genome screen of this family was reanalysed with only individuals CAE considered affected. Linkage analysis with performed using FASTLINK v4.0, two-point lod scores were calculated assuming 50% penetrance and a 2% phenocopy rate and individuals with FS or FS+ were coded as unknown. lod score greater than Markers producing a reanalysed without a phenocopy rate and at the observed penetrance for CAE in this family (30%). Results from the analysis revealed significant linkage to chromosome 14q22q23 (lod 3.4). This provides strong evidence for a second locus segregating with CAE affected individuals in this family. While the GABRG2 mutation is sufficient to cause FS, the CAE phenotype is thought to be due to both the

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GABRG2 mutation and a mutation occurring in a gene mapping to the 14q locus, as proposed by the digenic model.

For the application of the digenic model to sporadic cases of IGE and affected individuals belonging to smaller families in which genotyping and linkage analysis is not a feasible approach to disease gene identification, direct mutation analysis of ion channel genes in these individuals has been carried out as described above. In Table 1 there is provided an indication of novel genetic alterations so far identified through mutation analysis screening of these individuals. Figure 2 provides an example to indicate where some of these mutations have occurred with respect to the potassium channel KCNQ2 gene.

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The identification of novel mutations and variations in ion channel subunits in IGE individuals provides resources to further test the digenic hypothesis and mutation profiles are starting to accumulate for a number of subunit changes that are observed in the same individuals. Figure 3 provides results from some of these profiles.

Figure 3A shows a 3 generation family in which individual III-1 has myoclonic astatic epilepsy contains a N43del mutation in the SCN3A gene as well as an A1067T mutation in the SCN1A gene. Individual I-1 also has the SCN3A mutation but alone this mutation sufficient to cause epilepsy in this individual. The SCN3A mutation has likely been inherited from the grandfather through the mother, while the SCN1A mutation is likely to arise from the father. Both parents are unaffected but have yet to be screened for the presence of the mutations in these subunits. Individual II-1 is likely to contain an as yet unidentified ion channel subunit mutation acting in co-operation with the SCN3A mutation already identified in this individual.

Figure 3B is another 3 generation family in which individual III-1 has myoclonic astatic epilepsy due to a combination of the same SCN3A and SCN1A mutations as

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above. However, in this family both parents have febrile seizures most likely due to the presence of just one of the mutations in each parent, as proposed by the model. This is in contrast to individuals II-2 and II-3 in Figure 4A who also contain one of the mutations in these genes each. These individuals are phenotypically normal most likely due to incomplete penetrance of these mutations in each case.

Figure 3C shows a larger multi-generation family in which individual IV-5 has a mutation in both the SCN3A and GABRG2 subunits. In combination, these give rise to severe myoclonic epilepsy of infancy but alone either cause febrile seizures (GABRG2 mutation in III-3 and IV-4) or are without an effect (SCN3A mutation in III-2) as proposed by the model.

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These examples therefore illustrate the digenic model as determined from mutation analysis studies of ion channel subunits in affected individuals and highlight the need to identify genetic alterations in the genes encoding ion channel subunits.

Example 5: Analysis of ion channels and ion channel subunits

The structure and function of the mutant ion channels and mutant ion channel subunits of the present invention 25 can be determined using a variety of molecular biological studies. These studies may provide clues as to mechanisms by which mutations in ion channel subunits effect the functioning of the ion channel. For instance the identification of proteins that interact with mutant 30 (or whose interaction ion channels is impeded by a mutation in an ion channel subunit) may help determine the molecular mechanisms that are disrupted as a result of a mutation. Procedures such as the yeast two-hybrid system can be used to discover and identify such interacting 35 proteins.

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The principle behind the yeast two-hybrid procedure many eukaryotic transcriptional activators, is including those in yeast, consist of two discrete modular domains. The first is a DNA-binding domain that binds to a specific promoter sequence and the second is an activation domain that directs the RNA polymerase II complex to transcribe the gene downstream of the DNA binding site. Both domains are required for transcriptional activation as neither domain can activate transcription on its own. In the yeast two-hybrid procedure, the gene of interest or parts thereof (BAIT), is cloned in such a way that it is expressed as a fusion to a peptide that has a DNA binding domain. A second gene, or number of genes, such as those from a cDNA library (TARGET), is cloned so that it is expressed as a fusion to an activation domain. Interaction of the protein of interest with its binding partner brings the DNA-binding peptide together with the activation domain and initiates transcription of the reporter genes. The first reporter gene will select for yeast cells that contain interacting proteins (this reporter is usually a nutritional gene required for growth on selective media). The second reporter is used for confirmation and while being expressed in response to interacting proteins it is usually not required for growth.

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KCNQ2 interactors

Despite the identification of a number of KCNQ2 mutations responsible for epilepsy, including those of the underlying biological mechanisms study, the present epilepsy remains responsible for the uncharacterized. Towards identifying these mechanisms, large intracellular C-terminal region of KCNQ2 screened for interactions with other proteins using the yeast-two hybrid procedure. The C-terminus accounts 63% of the KCNQ2 protein and, in common with other KCNQ subunits, contains a conserved 'A domain' (Jentsch, 2000; Schwake et al., 2000) thought to be involved in subunit

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interactions as well as another distal short conserved region that has been associated with subunit assembly, at least in KCNQ1 (Jentsch, 2000; Schmitt et al., 2000).

5 A) Yeast-two hybrid analysis

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A yeast two-hybrid screen was carried out using the ProOuestTM Two-Hybrid System with Gateway™ Technology (Invitrogen TM) according to manufacturer's directions. A KCNQ2 C-terminal entry (BAIT) clone was generated using the pENTR Directional TOPO $^{\otimes}$ Cloning Kit (Invitrogen $^{\text{TM}}$). The following primers were designed to amplify intracellular C-terminal region of KCNQ2 based on sequence of human KCNQ2 (Genbank accession NM 172107): KCNQ2F: 5'-CACCAAGGTTCAGGAGCAGCACAGG-3' KCNQ2R: 5'-TCACTTCCTGGGCCCGGCCCAGCC-3'. The 1611 base pair cloned fragment included exon 10a (found in all amplified clones), corresponding to amino acid 373-382 of the KCNQ2 protein. The extra 30 base pairs (10 amino acids) were included in our numbering. The PCR-product was cloned into the pENTR/D-TOPO $^{\textcircled{\tiny{\$}}}$ vector (Invitrogen $^{\texttt{TM}}$) via the TOPO® Cloning reaction according to the manufacturer's instructions. Following sequence verification, the KCNQ2 cDNA fragment was then subcloned into pDEST $^{\text{TM}}$ 32, the DNA Binding domain (DB) $\mathsf{Gateway}^{\mathsf{TM}}$ Destination Vector (Invitrogen™).

The ProQuestTM Two-Hybrid human brain cDNA Library (TARGET) with GatewayTM technology (ResGenTM, InvitrogenTM Corporation) was amplified according to the manufacturer's instructions. Plasmid DNA was purified from the cell pellet using the HiSpeed Plasmid Maxi Kit (Qiagen) according to the manufacturer's instructions.

Both the DBLeu (empty bait vector) and DB-KCNQ2 wild-type (wt) C-term BAITS were transformed into the yeast strain Mav203 and plated onto minimal selective media lacking leucine. A duplicate was carried out where the empty library TARGET (pAD) vector was co-transformed in addition to each BAIT and plated onto minimal selective

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media lacking leucine (-leu) and tryptophan (-tryp). Yeast control strains (InvitrogenTM) were included on all plates. Control 1, used as a negative control, contained empty plasmids pPC97 and pPC86. Control 2 had pPC97-RB and pPC86-E2F1, which express a relatively weak interaction. Control 3 contained plasmids encoding the *Drosophila* DP (pPC97) and E2F (pPC86) domains that have a moderately strong interaction, and provide a control for plasmid shuffling. Control 4 contained pPC97-Fos and pPC86-Jun which express a relatively strong interaction, and control 5 had a pCL1 plasmid encoding full-length GAL4p and empty pPC86 and was used as a positive control.

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The constructs were tested for self-activation of the his and $\beta\text{-gal}$ reporter genes according to Invitrogen instructions.

For the yeast-two hybrid screen, competent yeast cells were prepared for each BAIT (DB-KCNQ2 wt C-term construct) to be screened, transformed with ProQuest™ Two-Hybrid human brain AD (activation domain) cDNA Library and plated onto minimal selective media lacking leucine (-leu), tryptophan (-tryp) and histidine (-his) and containing 3-aminotriazole (+3AT). Positive colonies from each screen were PCR-amplified and reintroduced into fresh yeast cells containing the BAIT to re-test for two-hybrid interaction phenotypes. qiving rise to more than one PCR product or that failed to re-test positively were systematically eliminated. Positives that re-tested were sequenced using the ABI BigDye™ Terminators v3.0 PRISM® technology. identified, the sequence of the potential interactor was checked to verify it was in the same translational frame as the Gal4p-AD encoding sequence of the prey construct.

Approximately 3 x 10^6 clones from the ProQuestTM Two-Hybrid human brain cDNA Library were screened for interaction with the DB-Q2C wt bait. Among 1039 positive AD-cDNAs recovered, re-tested and subsequently sequenced

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all were identified as the CALM2 gene, encoding the ubiquitous, Ca^{2+} -binding protein, Calmodulin (CaM).

The interaction between the C-terminal region of KCNQ2 and CaM has also been reported by other studies (Wen and Levitan, 2002; Yus-Najera et al., 2002; Gamper and Shapiro, 2003). In mammals, the CaM protein is coded by a multigene family consisting of three bona fide members, CALM1, CALM2 and CALM3. Within the non-coding regions of the CaM transcripts, no striking homology is observed, and codon usage is maximally divergent amongst the three CaM mRNAs that encode an identical protein. It has been hypothesised that the existence of a multigene family provides a tight and complex level of regulatory control at the level of gene expression (Palfi et al., 2002). CaM genes are differentially expressed in the CNS during development and differential regulation of the CaM genes appears necessary to maintain the temporal and spatial fidelity of the CaM protein levels in all subcellular domains. Besides the fundamental housekeeping functions associated with CaM, it is also involved in specialized neuronal functions, such as the synthesis and release of neurotransmitters, neurite extension, long-term potentiation and axonal transport (Palfi et al., 2002).

25 B) Effect of epilepsy-associated KCNQ2 mutations on the CaM-KCNQ2 interaction

To assess the effect that the C-terminus mutations of the present invention had on CaM binding, two of the identified mutations (R353G and L619R) were introduced into the DB-Q2C construct by mutagenesis and were reanalysed for an interaction with CaM using the yeast two-hybrid procedure.

The following primers were used to incorporate the c1057C \rightarrow G (R353G) and c1856T \rightarrow G (L619R) changes into the pDESTTM32- KCNQ2 C-terminal bait construct.

R353G F 5'-CGCCACCAACCTCTCGGGCACAGACCTGCACTC-3'

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R353G R 5'-GAGTGCAGGTCTGTGCCCGAGAGGTTGGTGGCG-3'

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L619R F 5'-CTTGTCCATGGAGAAGAGCGGGACTTCCTGGTGAATATC-3'

L619R R 5'-GATATTCACCAGGAAGTCCCGCTTCTTCTCCATGGACAAG-3'

Overlapping PCR products were generated using the TOPO® cloning compatible KCNQ2F primer from the initial cloning and the mutagenesis reverse primers, and the KCNQ2R primer from the initial cloning with the mutagenesis forward primers. Products were gel extracted and purified before a second round of PCR using the initial KCNQ2 F&R primers. These products were also gel extracted before cloning into the pDESTTM32 bait vector via the TOPO® system (as described above). Mutant baits were sequence verified.

The interaction between each DB-Q2C mutant and CaM was then tested by the yeast two-hybrid assay and compared to the interaction with DB-Q2 wt. Three different PCR-amplified CaM positive clones from the initial screen were re-introduced by gap-repair²⁰ into the prey vector (pPC86) in the yeast strain expressing either DB-Q2C wt, DB-Q2C mutants or the empty DBLeu vector, used as negative control.

CaM interaction with the DB-Q2C wt and mutants was then assessed by expression of the $\it HIS3$ and $\it LacZ$ reporter genes.

The Q2C R353G mutant did not interact with CaM, as seen by no growth on HIS3 selective plate (Figure 4C) and no blue readout in the LacZ filter assay (seen as dark squares in Figure 4D-F). On the other hand, the DB-Q2C L619R mutant was shown to still interact with CaM, as seen by growth on HIS3 selective plate (Figure 4C) and the blue readout in the LacZ filter assay. Interestingly, the DB-Q2C L619R mutant showed an even greater growth level on HIS3 selective plate than the DB-Q2C wt and also appeared to stain faster and more intensely blue in the LacZ filter assay, suggesting a stronger interaction between CaM and this mutant.

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In order to better quantify β -gal activity, a second assay was carried out using the high sensitivity substrate Chlorophenol Red- β -D-Galactopyranoside (CPRG) in liquid culture. The affinity of the DB-Q2C/AD-CaM interaction was measured in terms of units of β -gal activity, with a zero value indicating no expression of the LacZ reporter gene, and hence no interaction.

In the CPRG assay, a value of 0.05 units β -gal activity (Figure 5) was significantly different from the empty bait vector replicate (P<0.01, Student's t test), confirming the interaction of the DB-Q2C wt with CaM.

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As observed in the LacZ filter assay, the CPRG assay showed a significant difference in the interaction between the Q2C R353G mutant and CaM as compared to the wt replicate (P<0.01, Student's t test, Figure 4).

These results suggest that the R353G mutation alters the structural conformation of the KCNQ2 C-terminal domain such that it is no longer able to bind to CaM and that this single point mutation is sufficient to abolish the interaction. By abolishing CaM binding, the R353G mutation could lead to an impairment of M-current *in vivo* due to decreased opening of the channel.

In contrast, the CPRG assay for the L619R Q2C mutant showed a significantly higher level of β -gal activity units (0.26 units) than the wt replicate (P<0.001, Student's ttest, Figure 5). This finding indicates that the L619R mutation alters the conformation of the protein in manner that increases CaM binding affinity for the KCNQ2 C-terminal domain by approximately 5-fold. The increased affinity for CaM may affect the ability of the complex to change conformation normally in response to calcium signalling. Alternatively, the marked increase in binding KCNQ2 CaM to the L619R mutant channel detrimental to the M-channel function via disruption of normal neuronal inhibitory/excitatory therefore causing the seizures associated with epilepsy, particularly BFNS. CaM is known to be involved in both the

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excitatory and inhibitory neurotransmission pathways (Ohya and Botstein, 1994) and it has been proposed that the temporal and spatial restrictions on CaM itself could enable the tight control of these opposing reactions (Toutenhoofd and Strehler, 2000). Hence, the KCNQ2 L619R mutation could lead to a disruption of the local CaM pool consequently disturbing the finely balanced excitatory and inhibitory neurotransmission systems.

These results implicate CaM in the pathogenesis of epilepsy and specifically in the BFNS syndrome. Whilst further work will be required to fully elucidate the involvement of the KCNQ2-CaM interaction in neuronal excitability and its correlation with idiopathic epilepsy, these data suggest that dysfunction of this interaction leads to aberrant neuronal excitability in some BFNS patients.

The calmodulin gene (and other ion channel interacting genes) may therefore be a target for mutation in epilepsy as well as other disorders associated with ion channel dysfunction. A mutation in an ion channel interacting gene when expressed alone, or when expressed in combination with one or more other ion channel mutations or ion channel interacting gene mutations (based on the digenic model), may give rise to the disorder. The nature of the ion channel interacting genes and proteins can be studied such that these partners can also be targets for drug discovery.

Industrial Applicability

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The mutant ion channel receptor subunits of the invention are useful in the diagnosis and treatment of diseases such as epilepsy and disorders associated with ion channel dysfunction including, but not limited to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic ataxia, migraine, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia,

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anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness and total colour-blindness.

- 74 -TABLE 1

Examples of mutations and variations identified in ion channel subunit genes

Subunit Gene	Exon/Intron	DNA Mutation	Amino Acid Change	SEQ ID
		Divi Matanon	- Immo rata chango	NOS
Sodium Chang				
_	variants – amino a	•	Dagay	. 70
SCN1A ^r	Exon 5	c664C→T	R222X	1, 73
SCN1A ^r	Exon 8	c1152G→A	W384X	2, 74
SCN1A ^r	Exon 9	c1183G→C	A395P	. 3, 75
SCN1A ^r	Exon 9	c1207T→C	F403L	4, 76
SCN1A ^r	Exon 9	c1237T→A	Y413N	5, 77
SCN1A ^r	Exon 9	c1265T→A	V422E	6, 78
SCN1A ^r	Exon 21	c4219C→T	R1407X	7, 79
SCN1A ^r	Exon 26	c5339T→C	M1780T	8, 80
SCN1A ^r	Exon 26	c5674C→T	R1892X	9, 81
SCN1B ^r	Exon 3	c254G→A	R85H	10, 82
SCN2A ^r	Exon 6A	c668G→A	R223Q	11, 83
SCN2A ^r	Exon 16	c2674G→A	V892I	12, 84
SCN2A ^r	Exon 17	c3007C→A	L1003I	13, 85
SCN2A ^r	Exon 19	c3598A→G	T1200A	14, 86
SCN2A ^r	Exon 20	c3956G→A	R1319Q	15, 87
Coding exonic	variants – no amir	no acid change		
SCN2A°	Exon 12	c1785T→C	-	16
SCN2A°	Exon 27	c4919T→A	-	17
Non-coding var	riants			
SCN1A ^r	Intron 9	IVS9-1G→A	-	18
SCN1A ^c	Intron 23	IVS23+33G→A	-	19
SCN2Ar .	Intron 7	IVS7+61T→A	-	20
SCN2A ^r	Intron 19	IVS19-55A→G	-	21
SCN2A ^r	Intron 22	IVS22-31A→G	-	22
SCN2A ^c	Intron 2	IVS2-28G→A	<u></u>	23
SCN2A ^c	Intron 8	IVS8-3T→C	-	24
SCN2A ^c	Intron 11	IVS11+49A→G	-	25
SCN2A ^c	Intron 11	IVS11-16C→T	-	26
SCN2A ^c	Intron 17	IVS17-71C→T	-	27
SCN2A ^c	Intron 17	IVS17-74delG	=	28
SCN2A ^c	Intron 17	IVS17-74insG	-	29
Nicotinic Acety	ylcholine Recepto	or Subunits		
	variants – amino a			
CHRNA5 ^r	Exon 4	c400G→A	V134I	30, 88
CHRNA2°	Exon 4	c373G→A	A125T	31, 89
CHRNA3°	Exon 2	c110G→A	R37H	32, 90
	s – no amino acid		25/11	22, 70
CHRNA2°	Exon 4	c351C→T	-	33
CHRNA2°	Exon 5	c771C→T	- -	34
CHRNA3°	Exon 2	c159A→G	<u>-</u> -	35
CHRNA3°	Exon 2 Exon 4		-	36
		c291G→A	-	
CHRNA3°	Exon 4	c345G→A	-	37

TABLE 1 (Continued)

Examples of mutations and variations identified in ion channel subunit genes

Examples of mutations and variations identified in foil channel subunit genes				
Subunit Gene	Exon/Intron	DNA Mutation	Amino Acid Change	SEQ ID NOS
Non-coding va	riants			
CHRNA2°	Intron 3	IVS3-16C→T	-	38
CHRNA3°	Intron 3	IVS3-5T→C	-	39
CHRNA3°	Intron 4	IVS4+8G→C	-	40
Potassium Ch	annel Subunits			•
Coding exonic	variants – amino	acid change		
KCNQ2 ^r	Exon 1	c204-c205insC	K69fsX119	41,91
KCNQ2 ^r	Exon 1	c1A→G	M1V	42
KCNQ2 ^r	Exon 1	c2T→C	M1T	43
KCNQ2 ^r	Exon 8	c1057C→G	R353G	44, 92
KCNQ2 ^r	Exon 11	c1288C→T	R430X	45, 93
KCNQ2 ^r	Exon 14	c1710A→T	R570S	46, 94
KCNQ2 ^r	Exon 15	c1856T→G	L619R	47, 95
Non-coding va	riants			•
KCNQ2 ^r	Intron 9	IVS9+(46-48)delCCT	-	48
KCNQ3 ^r	Intron 11	IVSÌ1+43G→A	-	49
KCNQ3°	Intron 12	· IV\$12+29G→A		50
GABA Recept	tor Subunits			
	variants – no am	ino acid change		
GABRB1 ^r	Exon 5	c508C→T	~	51
GABRB1 ^r	Exon 9	c1329G→A	-	52
GABRB1°	Exon 8	c975C→T	-	53
GABRG3°	Exon 8	c995T→C	_	54
Non-coding va				
GABRA1°	5' UTR	c-142A→G	-	55
GABRA1°	5' UTR	c-31C→T	_	56
GABRA2°	3' UTR	c1615G→A	-	57
GABRA5°	5' UTR	c-271G→C	<u></u>	58
GABRA5°	5' UTR	c-228A→G	_	59
GABRA5°	5' UTR	c-149G→C	<u></u>	60
GABRB2 ^b	5° UTR	c-159C→T	_	61
GABRB2°	3' UTR	c1749C→T	~	62
GABRPi ^c	5' UTR	c-101C→T	_	63
GABRB1°	Intron 1	IVS1+24T→G	-	64
GABRB1°	Intron 5	IVS6+72T→G	_	65
GABRB1°	Intron 7	IVS7-34A→G	_	66
GABRB3 ^r	Intron 1	IVS1-14C→T	-	67
GABRB3 ^r	Intron 7	IVS7+58delAA	-	68
GABRB ^r	Intron 6	IVS6+132insC	-	69
GABRD ^r	Intron 6	IVS6+130insC	-	70
GABRD ^r	Intron 6	IVS6+73del	_	71
GADAD	ind on o	CGCGCCCACCGCCCCT	TCCGCG	
GABRĠ3°	Intron 8	IVS8-102C→T	•	72

GABRG3^c Intron 8 IVS8-102C→T - 72

Note: Mutations or variations only occurring in individuals with epilepsy; Variant seen only in normal control samples; Mutations or variants seen in individuals with epilepsy as well as normal control samples. The KCNQ2 numbering is based on the large isoform (inclusion of exon 10a). The numbering of exons and introns for SCNRA is based on the publication of Kassi et al. 2001.

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Claims

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1. A method of identifying a subject predisposed to a disorder associated with ion channel dysfunction, comprising ascertaining whether at least one of the genes encoding ion channel subunits in said subject has undergone a mutation event selected from the group consisting of the mutation events set forth in the following Table:

following	Table:	
Subunit Gene	Exon/Intron	DNA Mutation
SCN1A	Exon 5	c664C→T
SCN1A	Exon 8	c1152G→A
SCN1A	Exon 9	c1183G→C
SCN1A	Exon 9	c1207T→C
SCN1A	Exon 9	c1237T→A
SCN1A	Exon 9	c1265T→A
SCN1A	Exon 21	c4219C→T
SCN1A	Exon 26	c5339T→C
SCN1A	Exon 26	c5674C→T
SCN1B	Exon 3	c254G→A
SCN2A	Exon 6A	C668G→A
SCN2A	Exon 16	c2674G→A
SCN2A	Exon 17	c3007C→A
SCN2A	Exon 19	c3598A→G
SCN2A	Exon 20	c3 % 56G→A
SCN2A	Exon 12	c1785T→C
SCN2A	Exon 27	c4919T→A
SCN1A	Intron 9	IVS9-1G→A
SCN1A	Intron 23	IVS23+33G→A
SCN2A	Intron 7	IVS7+61T→A
SCN2A	Intron 19	IVS19-55A→G
SCN2A	Intron 22	IVS22-31A→G
SCN2A	Intron 2	IVS2-28G→A
SCN2A	Intron 8	IVS8-3T→C
SCN2A	Intron 11	IVS11+49A→G
SCN2A	Intron 11	IVS11-16C→T
SCN2A	Intron 17	IVS17-71C→T
SCN2A	Intron 17	IVS17-74delG
SCN2A	Intron 17	IVS17-74insG
CHRNA5	Exon 4	c400G→A
CHRNA2	Exon 4	c373G→A
CHRNA3	Exon 2	c110G→A
CHRNA2	Exon 4	c351C→T

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CHRNA2	Exon 5	c771C→T
CHRNA3	Exon 2	c159A→G
CHRNA3	Exon 4	c291G→A
CHRNA3	Exon 4	c345G→A
CHRNA2	Intron 3	IVS3-16C→T
CHRNA3	Intron 3	IVS3-5T→C
CHRNA3	Intron 4	IVS4+8G→C
KCNQ2	Exon 1	c204-c205insC
KCNQ2	Exon 1	c1A→G
KCNQ2	Exon 1	C2T→C
KCNQ2	Exon 8	c1057C→G
KCNQ2	Exon 11	c1288C→T
KCNQ2	Exon 14	C1710A→T
KCNQ2	Exon 15	c1856T→G
KCNQ2	Intron 9	IVS9+(46-48)delCCT
KCNQ3	Intron 11	IVS11+43G→A
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GABRB1	Exon 5	c508C→T
GABRB1	Exon 9	c1329G→A
GABRB1	Exon 8	c975C→T
GABRG3	Exon 8	c995T → C
GABRA1	5' UTR	c-142A→G
GABRA1	5' UTR	C-31C→T
GABRA2	3' UTR	c1615G→A
GABRA5	5' UTR	c-271G→C
GABRA5	5' UTR	c-228A→G
GABRA5	5' UTR	c-149G→C
GABRB2	5' UTR	c-159C→T
GABRB2	3' UTR	c1749C→T
GABRPi	5' UTR	C-101C→T
GABRB1	Intron 1	IVS1+24T→G
GABRB1	Intron 6	IVS6+72T→G
GABRB1	Intron 7	IVS7-34A→G
GABRB3	Intron 1	IVS1-14C→T
GABRB3	Intron 7	IVS7+58delAA
		<u>.</u>
GABRD	Intron 6	IVS6+132insC
GABRD	Intron 6	IVS6+130insC
GABRD GABRG3	Intron 6 Intron 8	IVS6+73delCGCGCCCACCGCCCTTCCGCG
GADIGO	TILLIOI	IVS8-102C→T

2. A method as claimed in claim 1 wherein a cDNA derived from said subject comprises the sequence set forth in one of SEQ ID NOS: 1-72.

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- 3. A method as claimed in claim 1 wherein a cDNA derived from said subject has the sequence set forth in one of SEQ ID NOS: 1-72.
- 5 4. A method as claimed in any one of claims 1 to 3, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce an epilepsy phenotype in said subject.
- A method as claimed in any one of claims 1 to 3, 10 5. wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce one or more with ionchannel dysfunction, disorders associated including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, 15 cardiac arrhythmias, episodic ataxia, myasthenia, Alzheimer's disease, Parkinson's disease, migraine, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney 20 disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness and total colour-blindness in said subject.
- 25 6. A method as claimed in any one of claims 1 to 3, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce an epilepsy phenotype when expressed in combination with one or more additional mutations or variations in said ion channel subunit genes.
 - 7. A method as claimed in any one of claims 1 to 3, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce one or more disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia,

myasthenia, cardiac arrhythmias, episodic ataxia, migraine, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness and total colour-blindness, when expressed in combination with one or more additional mutations or variations in said ion channel subunit genes.

8. An isolated nucleic acid molecule encoding a mutant or variant ion channel subunit wherein a mutation event selected from the group consisting of the mutation events

15 set forth in the following Table:

5

set forth	in the following	Table:
Subunit Gene	Exon/Intron	DNA Mutation
SCN1A	Exon 5	c664C→T
SCN1A	Exon 8	c1152G→A
SCN1A	Exon 9	c1183G→C
SCN1A	Exon 9	c1207T→C
SCN1A	Exon 9	c1237T→A
SCN1A	Exon 9	c1265T→A
SCN1A	Exon 21	C4219C→T
SCN1A	Exon 26	c5339T→C
SCN1A	Exon 26	c5674C→T
SCN1B	Exon 3	c254G→A
SCN2A	Exon 6A	c668G→A
SCN2A	Exon 16	c2674G→A
SCN2A	Exon 17	c3007C→A
SCN2A	Exon 19	c3598A→G
SCN2A	Exon 20	c3956G→A
SCN2A	Exon 12	c1785T→C
SCN2A	Exon 27	C4919T→A
SCN1A	Intron 9	IVS9-1G→A
SCN1A	Intron 23	IVS23+33G→A
SCN2A	Intron 7	IVS7+61T→A
SCN2A	Intron 19	IVS19-55A→G
SCN2A	Intron 22	IVS22-31A→G
SCN2A	Intron 2	IVS2-28G→A
SCN2A	Intron 8	IVS8-3T→C
SCN2A	Intron 11	IVS11+49A→G
SCN2A	Intron 11	IVS11-16C→T

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SCN2A	Intron 17	IVS17-71C→T
SCN2A	Intron 17	IVS17-74delG
SCN2A	Intron 17	IVS17-74insG
CHRNA5	Exon 4	C400G→A
CHRNA2	Exon 4	c373G→A
CHRNA3	Exon 2	c110G→A
CHRNA2	Exon 4	c351C→T
CHRNA2	Exon 5	c771C→T
CHRNA3	Exon 2	c159A→G
CHRNA3	Exon 4	c291G→A
CHRNA3	Exon 4	c345G→A
CHRNA2	Intron 3	IVS3-16C→T
CHRNA3	Intron 3	IVS3-5T→C
CHRNA3	Intron 4	IVS4+8G→C
KCNQ2	Exon 1	c204-c205insC
KCNQ2	Exon 1	c1A→G
KCNQ2	Exon 1	c2T→C
KCNQ2	Exon 8	c1057C→G
KCNQ2	Exon 11	c1288C→T
KCNQ2	Exon 14	C1710A→T
KCNQ2	Exon 15	c1856T→G
KCNQ2	Intron 9	IVS9+(46-48)delCCT
KCNQ3	Intron 11	IVS11+43G→A
KCNQ3	Intron 12	IVS12+29G→A
GABRB1	Exon 5	c508C→T
GABRB1	Exon 9	c1329G→A
GABRB1	Exon 8	c975C→T
GABRG3	Exon 8	c995T→C
GABRA1	5' UTR	c-142A→G
GABRA1	5' UTR	c-31C→T
GABRA2	3' UTR	c1615G→A
GABRA5	5' UTR	c-271G→C
GABRA5	5' UTR	c-228A→G
GABRA5	5' UTR	c-149G→C
GABRB2	5' UTR	c-159C→T
GABRB2	3' UTR	c1749C→T
GABRPi	5' UTR	c-101C→T
GABRB1	Intron 1	IVS1+24T→G
GABRB1	Intron 6	IVS6+72T→G
GABRB1	Intron 7	IVS7-34A→G
GABRB3	Intron 1	IVS1-14C→T
GABRB3	Intron 7	IVS7+58delAA
GABRD	Intron 6	IVS6+132insC
GABRD	Intron 6	IVS6+130insC
GABRD	Intron 6	IVS6+73delCGCGCCCACCGCCCCTTCCGCG
GABRG3	Intron 8	IVS8-102C→T

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has occurred.

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9. An isolated nucleic acid molecule encoding a mutant or variant ion channel subunit as claimed in claim 8 wherein a cDNA derived therefrom comprises the sequence set forth in one of SEQ ID NOS: 1-72.

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- 10. An isolated nucleic acid molecule encoding a mutant or variant ion channel subunit as claimed in claim 8 wherein a cDNA derived therefrom has the sequence set forth in one of SEQ ID NOS: 1-72.
- 11. An isolated nucleic acid molecule encoding a mutant or variant ion channel subunit as claimed in any one of claims 8 to 10, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce an epilepsy phenotype.
- 12. An isolated nucleic acid molecule encoding a mutant or variant ion channel subunit as claimed in any one of 20 claims 8 to 10, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce more disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant 25 hyperthermia, myasthenia, cardiac arrhythmias, ataxia, migraine, Alzheimer $^\prime$ s disease, Parkinson's schizophrenia, hyperekplexia, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, 30 disease, Dent's polycystic kidney hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness and total colourblindness.
 - 13. An isolated nucleic acid molecule encoding a mutant or variant ion channel subunit as claimed in any one of

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claims 8 to 10, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce an epilepsy phenotype when expressed in combination with one or more additional mutations or variations in said ion channel subunit genes.

An isolated nucleic acid molecule encoding a mutant or variant ion channel subunit as claimed in any one of claims 8 to 10, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce more disorders associated with ionone orchannel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, migraine, Alzheimer's disease, Parkinson's ataxia, hyperekplexia, disease, schizophrenia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness and total colourblindness, when expressed in combination with one or more additional mutations or variations in said ion channel subunit genes.

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- 15. An isolated nucleic acid molecule comprising any one of the nucleotide sequences set forth in SEQ ID NOS: 1-72.
- 16. An isolated nucleic acid molecule consisting of any one of the nucleotide sequences set forth in SEQ ID NOS: 1-72.
- 17. An isolated nucleic acid molecule encoding a mutant KCNQ2 subunit, wherein the mutation event has occurred in the C-terminal domain of the KCNQ2 subunit and leads to a disturbance in the calmodulin binding affinity of the subunit, so as to produce an epilepsy phenotype.

18. An isolated nucleic acid molecule as claimed in claim 17 wherein the mutation event has occurred in exon 8, exon 11, exon 14 or exon 15.

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19. An isolated polypeptide, said polypeptide being a mutant or variant ion channel subunit wherein a mutation event selected from the group consisting of the mutation events set forth in the following Table:

et	forth	in	the	following Table:	
	Subun	it		Amino Acid Change	
	Gene			Amilio Acid Change	
	SCN1	Ā		R222X	
	SCN1	\mathcal{L}		W384X	
	SCN1	A.		A395P	
	SCN1	\mathcal{L}		F403L	
	SCN1	Ą		Y413N	
	SCN1	£		V422E	
	SCN1	Ą		R1407X	
	SCN1	A		M1780T	
	SCN1	A		R1892X	
	SCN1	3		R85H	
	SCN2	A		R223Q	
	SCN2	A		V892I	
	SCN2	A		L1003I	
SCN2A			T1200A		
SCN2A			R1319Q		
CHRNA5			V134I		
CHRNA2			Al25T		
	CHRNA	.3		R37H	
	KCNQ2	2		K69fsX119	
	KCNQ2	2		M1V	
	KCNQ2	2		M1T	
	KCNQ2			R353G	
	KCNQ2	2		R430X	
	KCNQ2	2		R570S	
	KCNQ2	2		L619R	

10 has occurred.

- 20. An isolated polypeptide, said polypeptide being a mutant or variant ion channel subunit as claimed in claim 19 wherein the polypeptide comprises the amino acid sequence set forth in one of SEQ ID NOS: 73-95.
- 21. An isolated polypeptide, said polypeptide being a mutant or variant ion channel subunit as claimed in claim

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- 19 wherein the polypeptide has the amino acid sequence set forth in one of SEQ ID NOS: 73-95.
- 22. An isolated polypeptide, said polypeptide being a mutant or variant ion channel subunit as claimed in any one of claims 19 to 21, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce an epilepsy phenotype.

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- 10 23. An isolated polypeptide, said polypeptide being a mutant or variant ion channel subunit as claimed in any one of claims 19 to 21, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce one or more disorders associated with ion channel dysfunction, including but not restricted to, 15 hypo-kalemic periodic paralysis, malignant hyperthermia, myasthenia, cardiac arrhythmias, ataxia, migraine, Alzheimer's episodic schizophrenia, Parkinson's disease, hyperekplexia, depression, phobic obsessive 20 anxiety, symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness and total colour-blindness. 25
 - 24. An isolated polypeptide, said polypeptide being a mutant or variant ion channel subunit as claimed in any one of claims 19 to 21, wherein said mutation event disrupts the functioning of an assembled ion channel so as to produce an epilepsy phenotype when expressed in combination with one or more additional mutations or variations in said ion channel subunit genes.
- 35 25. An isolated polypeptide, said polypeptide being a mutant or variant ion channel subunit as claimed in any one of claims 19 to 21, wherein said mutation event

- 90 - disrupts the functioning of an assembled ion channel so as

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to produce one or more disorders associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, 5 ataxia, migraine, Alzheimer's episodic schizophrenia, disease, hyperekplexia, Parkinson's phobic obsessive depression, anxiety, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's 10 disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness and total colour-blindness, when expressed in combination with one or more additional mutations or variations in said ion 15 channel subunit genes.

- 26. An isolated polypeptide comprising any one of the amino acid sequences set forth in SEQ ID NOS: 73-95.
- 20 27. An isolated polypeptide consisting of any one of the amino acid sequences set forth in SEQ ID NOS: 73-95.
- 28. An isolated polypeptide, said polypeptide being a mutant KCNQ2 subunit, wherein the mutation event has occurred in the C-terminal domain of the KCNQ2 subunit and leads to a disturbance in the calmodulin binding affinity of the subunit, so as to produce an epilepsy phenotype.
- 29. An isolated polypeptide complex, said polypeptide complex being an assembled mammalian ion channel including an ion channel subunit comprising a polypeptide as defined in any one of claims 19 to 28.
- 30. An expression vector comprising a nucleic acid molecule as claimed in any one of claims 8 to 18.

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31. A cell comprising at least one expression vector as claimed in claim 30.

- 32. A cell as claimed in claim 31 comprising two or more expression vectors.
 - 33. A cell comprising at least one ion channel type, wherein the or each ion channel type incorporates at least one mutant polypeptide as claimed in any one claims 19 to 28.
 - 34. A cell as claimed in claim 33 comprising ion channels that incorporate two or more mutant polypeptides.
- 15 35. A cell as claimed in claim 33 comprising two or more ion channel types each incorporating one or more mutant polypeptides.
- 36. A method of preparing a polypeptide, comprising the 20 steps of:
 - (1) culturing cells as claimed in any one of claims 31 to 35 under conditions effective for polypeptide production; and
 - (2) harvesting the polypeptide.

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- 37. A polypeptide prepared by the method of claim 36.
- 38. An antibody which is immunologically reactive with an isolated polypeptide as claimed in any one of claims 19 to 28 or claim 37, or an isolated polypeptide complex as claimed in claim 29.
- 39. An antibody as claimed in claim 38 which is selected from the group consisting of a monoclonal antibody, a humanised antibody, a chimeric antibody or an antibody fragment including a Fab fragment, (Fab')2 fragment, Fv

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fragment, single chain antibodies and single domain antibodies.

- 40. A method of treating epilepsy comprising administering an antibody as claimed in either one of claims 38 or 39 to a subject in need of such treatment.
- 41. The use of an antibody, as claimed in either one of claims 38 or 39, in the manufacture of a medicament for the treatment of epilepsy.
- 42. A method of treating a disorder associated with ion channel dysfunction, including but not restricted to, hypo-kalemic periodic paralysis, hyper- or malignant hyperthermia, myasthenia, cardiac arrhythmias, 15 episodic ataxia, migraine, Alzheimer's Parkinson's disease, schizophrenia, hyperekplexia, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, 20 Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness, comprising administering an antibody as claimed in either one of claims 38 or 39 to a subject in need of such treatment. 25
- The use of an antibody, as claimed in either one of claims 38 or 39, in the manufacture of a medicament for the treatment of a disorder associated with ion channel 30 dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic migraine, Alzheimer's disease, Parkinson's ataxia, disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, 35 inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's

hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-

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5 44. A method of treating epilepsy comprising administering a selective agonist, antagonist or modulator of an ion channel when it has undergone a mutation event or combination of events as defined in any one of claims

19 to 28 to a subject in need of such treatment.

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blindness.

- 45. The use of a selective agonist, antagonist or modulator of an ion channel when it has undergone a mutation event as defined in any one of claims 19 to 28 in the manufacture of a medicament for the treatment of epilepsy.
- A method of treating a disorder associated with ion channel dysfunction, including but not restricted hypo-kalemic periodic paralysis, myotonias, hyper- or malignant hyperthermia, myasthenia, cardiac arrhythmias, 20 ataxia, migraine, Alzheimer's disease, episodic schizophrenia, hyperekplexia, Parkinson's disease, symptoms, phobic obsessive depression, anxiety, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's 25 disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness, comprising administering a selective agonist, antagonist or modulator of an ion channel when it has undergone a mutation event or combination of events as 30 defined in any one of claims 19 to 28 to a subject in need of such treatment.
- 47. The use of a selective agonist, antagonist or modulator of an ion channel when it has undergone a mutation event as claimed in any one of claims 19 to 28 in the manufacture of a medicament for the treatment of a

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disorder associated ${\tt with}$ ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic Alzheimer's disease, Parkinson's migraine, disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness.

48. A method of treating epilepsy comprising administering an isolated DNA molecule which is the complement (antisense) of a nucleic acid molecule as claimed in any one of claims 8 to 18 and which encodes an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 8 to 18, to a subject in need of such treatment.

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- 49. The use of a DNA molecule which is the complement of a nucleic acid molecule as claimed in any one of claims 8 to 18 and which encodes an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 8 to 18, in the manufacture of a medicament for the treatment of epilepsy.
- 50. A method of treating a disorder associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, 30 myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, ataxia, migraine, Alzheimer's episodic Parkinson's disease, schizophrenia, hyperekplexia, depression, phobic obsessive anxiety, 35 neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic

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fibrosis, congenital stationary night blindness or total colour-blindness, comprising administering an isolated DNA molecule which is the complement (antisense) of a nucleic acid molecule as claimed in any one of claims 8 to 18 and which encodes an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 8 to 18, to a subject in need of such treatment.

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- 51. The use of a DNA molecule which is the complement of 10 a nucleic acid molecule as claimed in any one of claims 8 to 18 and which encodes an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 8 to 18, in the manufacture of a medicament for the treatment of a disorder associated 15 with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, ataxia, migraine, Alzheimer's episodic 20 Parkinson's disease, schizophrenia, hyperekplexia, depression, phobic obsessive anxiety, symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, disease, hyperinsulinemic hypoglycemia of infancy, cystic 25 fibrosis, congenital stationary night blindness or total colour-blindness.
 - 52. A method of treating epilepsy comprising administering an antibody, as claimed in either one of claims 38 or 39, administration of an agonist, antagonist or modulator of an ion channel when it has undergone a mutation event or combination of events as defined in any one of claims 19 to 28, or administration of a DNA molecule which is the complement of a nucleic acid molecule as claimed in any one of claims 8 to 18 and which encodes an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one

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of claims 8 to 18, in combination with administration of the wild-type ion channel subunit, to a subject in need of such treatment.

- The use of an antibody, as claimed in claims 38 or 5 39, use of an agonist, antagonist or modulator of an ion it has undergone a mutation when event combination of events as defined in any one of claims 19 to 28, or use of a DNA molecule which is the complement of a nucleic acid molecule as claimed in any one of claims 8 10 to 18 and which encodes an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 8 to 18, in combination with the use of the wild-type ion channel subunit, in the manufacture of a medicament for the treatment of epilepsy. 15
 - 54. A method of treating a disorder associated with ion channel dysfunction, including but not restricted to, hypo-kalemic periodic paralysis, hyper- or malignant hyperthermia, myasthenia, cardiac arrhythmias, ataxia, migraine, Alzheimer's schizophrenia, hyperekplexia, Parkinson's disease, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness, comprising administering an antibody, claimed in either one of claims 38 administration of an agonist, antagonist or modulator of an ion channel when it has undergone a mutation event or combination of events as defined in any one of claims 19 to 28, or administration of a DNA molecule which is the complement of a nucleic acid molecule as claimed in any one of claims 8 to 18 and which encodes an RNA molecule that hybridizes with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 8 to 18, in

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combination with administration of the wild-type ion channel subunit, to a subject in need of such treatment.

- The use of an antibody, as claimed in claims 387 or 39, use of an agonist, antagonist or modulator of an ion 5 it has channel when undergone a mutation event combination of events as defined in any one of claims 19 to 28, or use of a DNA molecule which is the complement of a nucleic acid molecule as claimed in any one of claims 8 to 18 and which encodes an RNA molecule that hybridizes 10 with the mRNA encoded by a nucleic acid molecule as claimed in any one of claims 8 to 18, in combination with the use of the wild-type ion channel subunit, manufacture of a medicament for the treatment of a 15 disorder associated with ionchannel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic migraine, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, anxiety, depression, phobic 20 obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night 25 blindness or total colour-blindness.
 - 56. Use of a nucleic acid molecule as claimed in any one of claims 8 to 18 for the screening of candidate pharmaceutical agents.

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57. Use of a nucleic acid molecule as claimed in any one of claims 8 to 18 for the screening of candidate pharmaceutical agents useful for the treatment of epilepsy.

58. Use of a nucleic acid molecule as claimed in any one of claims 8 to 18 for the screening of candidate

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pharmaceutical agents useful for the treatment of a disorder associated with ionchannel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic Alzheimer's disease, Parkinson's migraine, disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness.

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- 59. Use of a polypeptide as claimed in any one of claims
 15 19 to 28 or claim 37, or a polypeptide complex as claimed
 in claim 29 for the screening of candidate pharmaceutical
 agents.
- 60. Use of a polypeptide as claimed in any one of claims
 20 19 to 28 or claim 37, or a polypeptide complex as claimed
 in claim 29 for the screening of candidate pharmaceutical
 agents useful for the treatment of epilepsy.
- 61. Use of a polypeptide as claimed in any one of claims 25 19 to 28 or claim 37, or a polypeptide complex as claimed in claim 29 for the screening of candidate pharmaceutical agents useful for the treatment of a disorder associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, 30 episodic ataxia, migraine, Alzheimer's Parkinson's disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's 35 disease, hyperinsulinemic hypoglycemia of infancy, cystic

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fibrosis, congenital stationary night blindness or total colour-blindness.

- 62. Use of a cell as claimed in any one of claims 31 to 35 for the screening of candidate pharmaceutical agents.
 - 63. Use of a cell as claimed in any one of claims 31 to 35 for the screening of candidate pharmaceutical agents useful for the treatment of epilepsy.

64. Use of a cell as claimed in any one of claims 31 to 35 for the screening of candidate pharmaceutical agents useful for the treatment of a disorder associated with ion channel dysfunction, including but not restricted to,

- hypo-kalemic periodic paralysis, myotonias, hyper- or 15 malignant hyperthermia, myasthenia, cardiac arrhythmias, Alzheimer's ataxia, migraine, episodic disease, schizophrenia, hyperekplexia, Parkinson's symptoms, phobic obsessive depression, anxiety,
- neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness.
 - 65. A compound when identified through a use as claimed in any one of claims 56 to 64.

- 66. A pharmaceutical composition comprising a compound as claimed in claim 65 and a pharmaceutically acceptable carrier.
- 67. A genetically modified non-human animal comprising an isolated nucleic acid molecule as claimed in any one of claims 8 to 18.

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68. A genetically modified, non-human animal which comprises two or more isolated nucleic acid molecules as claimed in any one of claims 8 to 18.

- 5 69. A genetically modified non-human animal as claimed in either one of claims 67 or 68 in which the animal is selected from the group consisting of rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs and non-human primates such as monkeys and chimpanzees.
 - 70. A method of producing a non-human transgenic animal comprising a combination of two or more ion channel mutations, comprising the steps of:

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- (1) creating a non-human transgenic animal comprising a first nucleic acid molecule as claimed in any one of claims 8 to 18;
- (2) creating one or more additional non-human, transgenic animals comprising a second nucleic acid molecule as claimed in any one of claims 8 to 18; and
- (3) conducting mating combinations so as to produce progeny containing combinations of two or more ion channel mutations which effectively mimic combinations of ion channel mutations responsible for human disease.
- 71. A non-human, transgenic animal produced by the process of claim 70.
- 72. The use of a genetically modified non-human animal as claimed in any one of claims 67 to 69 or a non-human transgenic animal as claimed in claim 71 in the screening of candidate pharmaceutical compounds.
- 73. The use of a genetically modified non-human animal as claimed in any one of claims 67 to 69 or a non-human

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transgenic animal as claimed in claim 71 in the screening of candidate pharmaceutical compounds useful in the treatment of epilepsy.

- The use of a genetically modified non-human animal as 5 74. claimed in any one of claims 67 to 69 or a non-human transgenic animal as claimed in claim 71 in the screening candidate pharmaceutical compounds useful disorder associated with ion channel treatment of a dysfunction, including but not restricted to, hyper- or 10 hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac arrhythmias, episodic Alzheimer's disease, Parkinson's ataxia, migraine, hyperekplexia, disease, schizophrenia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, 15 inflammatory pain, chronic/acute pain, Bartter's syndrome, disease, kidney disease, Dent's polycystic hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary night blindness or total colourblindness. 20
 - 75. The use of an isolated nucleic acid molecule as claimed in any one of claims 8 to 18 for the diagnosis or prognosis of epilepsy.

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The use of an isolated nucleic acid molecule as 76. claimed in any one of claims 8 to 18 for the diagnosis or a disorder associated with ion channel prognosis of dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant 30 hyperthermia, myasthenia, cardiac arrhythmias, episodic Alzheimer's disease, Parkinson's migraine, hyperekplexia, schizophrenia, disease, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, 35 disease, Dent's kidney polycystic hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, WO 2005/014863 PCT/AU2004/001051
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congenital stationary night blindness or total colourblindness.

- 77. The use of a polypeptide as defined in any one of claims 19 to 28 or claim 37, or polypeptide complex as claimed in claim 29 in the diagnosis or prognosis of epilepsy.
- The use of a polypeptide as defined in any one of claims 19 to 28 or claim 37, or polypeptide complex as 10 claimed in claim 29 in the diagnosis or prognosis of a disorder associated with ionchannel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, cardiac arrhythmias, myasthenia, episodic 15 migraine, Alzheimer's disease, Parkinson's disease, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of 20 infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness.
- 79. The use of an antibody as claimed in either one of claims 38 or 39 in the diagnosis or prognosis of epilepsy.
- The use of an antibody as claimed in either one of claims 38 or 39 in the diagnosis or prognosis of a with ion channel associated dysfunction, including but not restricted to, hyper- or hypo-kalemic 30 periodic paralysis, myotonias, malignant hyperthermia, cardiac arrhythmias, episodic myasthenia, Alzheimer's disease, Parkinson's migraine, schizophrenia, hyperekplexia, anxiety, depression, phobic obsessive symptoms, neuropathic pain, inflammatory pain, 35 chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of

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infancy, cystic fibrosis, congenital stationary night blindness or total colour-blindness.

- 81. A method for the diagnosis or prognosis of epilepsy comprising the steps of:
 - (1) obtaining DNA from a subject; and
 - (2) comparing the DNA of one or more subunits of ion channels from said subject to the DNA of the corresponding native subunits;
- wherein identification of one or more DNA molecules as claimed in any one of claims 8 to 18 is an indication of epilepsy, or a predisposition thereto.
- A method for the diagnosis or prognosis of a disorder 82. 15 associated with ion channel dysfunction, including but not restricted to, hyper- or hypo-kalemic periodic paralysis, myotonias, malignant hyperthermia, myasthenia, cardiac ataxia, migraine, arrhythmias, episodic Alzheimer's disease, Parkinson's disease, schizophrenia, 20 hyperekplexia, anxiety, depression, phobic obsessive neuropathic pain, inflammatory pain, chronic/acute pain, Bartter's syndrome, polycystic kidney disease, Dent's disease, hyperinsulinemic hypoglycemia of infancy, cystic fibrosis, congenital stationary blindness or total colour-blindness, comprising the steps 25 of:
 - (1) obtaining DNA from a subject; and
 - (2) comparing the DNA of one or more subunits of ion channels from said subject to the DNA of the corresponding native subunits;

wherein identification of one or more DNA molecules as claimed in any one of claims 8 to 18 is an indication of the disorder, or a predisposition thereto.

35 83. A method as claimed in either one of claims 81 or 82 wherein each DNA fragment is sequenced and the sequences compared.

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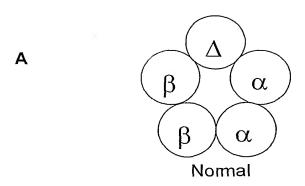
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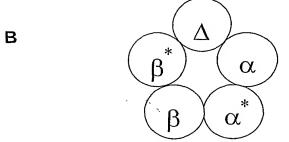
84. A method as claimed in either one of claims 81 or 82 wherein the DNA fragments are subjected to restriction enzyme analysis.

5

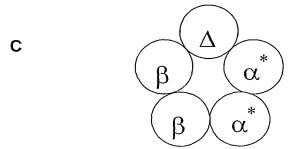
85. A method as claimed in either one of claims 81 or 82 wherein the DNA fragments are subjected to SSCP analysis.

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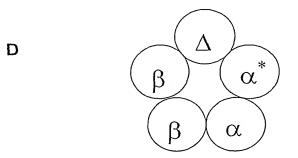




IGE: Outbred Population



IGE: Inbred Population



IGE: Autosomal Dominant

FIG. 1

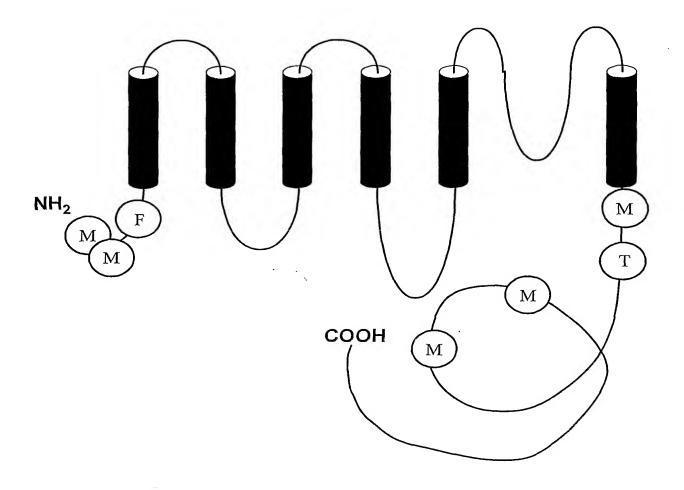


FIG. 2

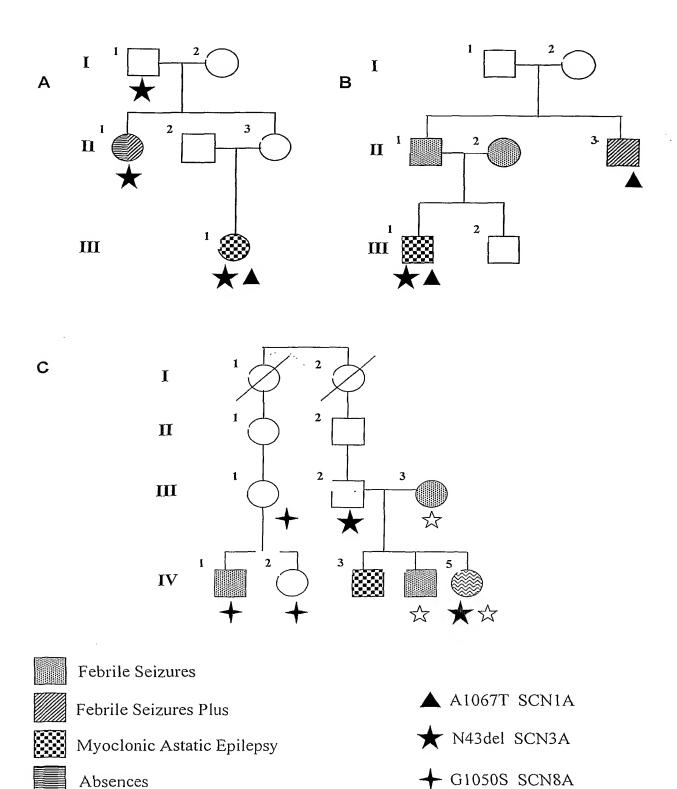


FIG. 3

☆ Q351X GABRG2

Severe Myoclonic Epilepsy of Infancy

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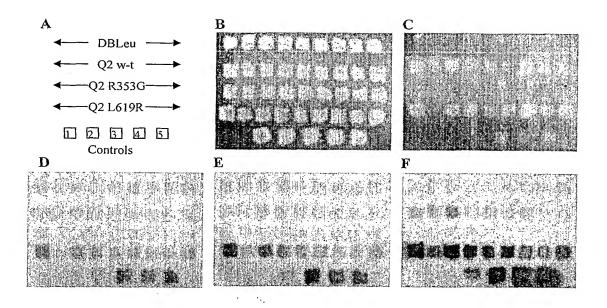


FIG. 4

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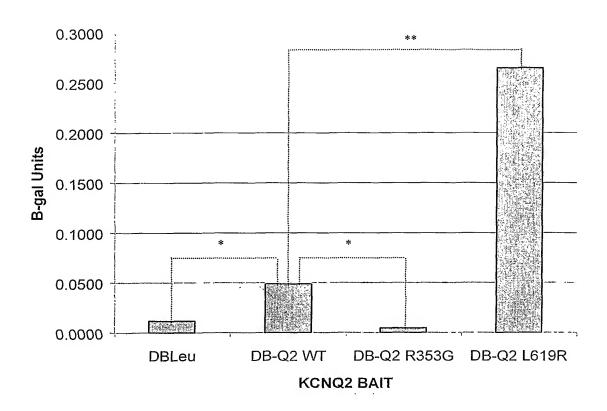


FIG. 5

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SSCP Undate Sequences ST25

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tgatgaa	ctt caagtccggt	aacatatgcc	cgccgcccct	tccgcatgtg	cccgccgccc	180
cttccgc	gcg cgcccaccgc	cccttccgcg	cgcgcccacc	gccccttccg	cgtgcgcccg	240
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ggctgga	.caa gctgcagctg	gcgcagttca	ccatcaccag	ctaccgcttc	accacggagc	120
tgatgaa	ctt caagtccggt	aacatatgcc	cgccgcccct	tccgcatgtg	cccgccgccc	180
cttccgc	gcg cgcccaccgc	cccttccgcg	tgcgcccgcc	tgtggttttc	atgcttttta	240
gtcaagc	gcc cgcaggcccc	cagggcctct	ggggatgcag	ctgggacg		288
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SSCP Update Sequences.ST25

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Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu 20 25 30

Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Asp Glu Asn Gly 40 45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile 50 55 60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu 65 70 75 80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu 85 90 95

Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr  $100 \hspace{1cm} 105 \hspace{1cm} 110$ 

Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser 115 120 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe 130 135 140

Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr 145 150 155 160

Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg 165 170 175

Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp 180 185 190

Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp 195 200 205

Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu 210 220

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SSCP Update Sequences.ST25 Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu 290 295 300

Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp 305 310 315

Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys 325 330 335

Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val 340 345 350

Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe 355 360 365

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Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu 20 25 30

Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Asp Glu Asn Gly 35 40 45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile 50 55 60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu 65 70 75 80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu 85 90 95

Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr  $100 \hspace{1cm} 105 \hspace{1cm} 110$ 

Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser 115 120 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe 130 140

Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr Page 124

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⁷⁵ 2009

PRT

Homo sapiens

PCT/AU2004/001051

WO 2005/014863

SSCP Update Sequences.ST25 145 150 160 Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg 165 170 175 Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp 180 185 190 Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp 195 200 205 Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu 210 220 Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu 225 230 235 240 Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe 245 250 255 Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn 260 265 270 Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu 275 280 285 Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu 290 295 300 Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp 305 310 315 320 Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys 325 330 335 Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val 340 345 350 Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe 355 360 365 Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp 370 375 380 Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Pro Gly Lys Thr Tyr Met 385 390 395 400 Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Ile Asn 405 410 415

Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala

WO 2005/014863

SSCP Update Sequences.ST25
420 425 430

PCT/AU2004/001051

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485 490 495 Arg Arg Asn Arg Arg Lys Lys Arg Lys Gln Lys Glu Gln Ser Gly Gly 500 505 Glu Glu Lys Asp Glu Asp Glu Phe Gln Lys Ser Glu Ser Glu Asp Ser 515 520 525 Ile Arg Arg Lys Gly Phe Arg Phe Ser Ile Glu Gly Asn Arg Leu Thr 530 540 Tyr Glu Lys Arg Tyr Ser Ser Pro His Gln Ser Leu Leu Ser Ile Arg 545 550 555 560 Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Thr Ser Leu Phe Ser 575 Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp Phe Ala Asp 580 585 590 Asp Glu His Ser Thr Phe Glu Asp Asn Glu Ser Arg Asp Ser Leu 595 600 605 Phe Val Pro Arg Arg His Gly Glu Arg Arg Asn Ser Asn Leu Ser Gln 610 620 Thr Ser Arg Ser Ser Arg Met Leu Ala Val Phe Pro Ala Asn Gly Lys 625 630 635 640 Met His Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Val Gly Gly 645 650 655 Pro Ser Val Pro Thr Ser Pro Val Gly Gln Leu Leu Pro Glu Val Ile 660 665 670 Ile Asp Lys Pro Ala Thr Asp Asp Asn Gly Thr Thr Glu Thr Glu 685 Met Arg Lys Arg Arg Ser Ser Ser Phe His Val Ser Met Asp Phe Leu Page 126

SSCP Update Sequences.ST25 690 695 700

Glu Asp Pro Ser Gln Arg Gln Arg Ala Met Ser Ile Ala Ser Ile Leu 705 710 715 720

PCT/AU2004/001051

Thr Asn Thr Val Glu Glu Leu Glu Glu Ser Arg Gln Lys Cys Pro Pro 725 730 735

Cys Trp Tyr Lys Phe Ser Asn Ile Phe Leu Ile Trp Asp Cys Ser Pro 740 745 750

Tyr Trp Leu Lys Val Lys His Val Val Asn Leu Val Val Met Asp Pro 755 760 765

Phe Val Asp Leu Ala Ile Thr Ile Cys Ile Val Leu Asn Thr Leu Phe 770 780

Met Ala Met Glu His Tyr Pro Met Thr Asp His Phe Asn Asn Val Leu 785 790 795 800

Thr Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Phe 805 810 815

Leu Lys Ile Ile Ala Met Asp Pro Tyr Tyr Tyr Phe Gln Glu Gly Trp 820 825 830

Asn Ile Phe Asp Gly Phe Ile Val Thr Leu Ser Leu Val Glu Leu Gly 835 840

Leu Ala Asn Val Glu Gly Leu Ser Val Leu Arg Ser Phe Arg Leu Leu 850 860

Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Met Leu Ile 865 870 875 880

Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val 885 890 895

Leu Ala Ile Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe 900 905 910

Gly Lys Ser Tyr Lys Asp Cys Val Cys Lys Ile Ala Ser Asp Cys Gln 915 920 925

Leu Pro Arg Trp His Met Asn Asp Phe Phe His Ser Phe Leu Ile Val 930 935 940

Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met 945 950 955 960

Glu Val Ala Gly Gln Ala Met Cys Leu Thr Val Phe Met Met Val Met Page 127 WO 2005/014863

SSCP Update Sequences.ST25 965 970 975

PCT/AU2004/001051

Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu 980 985 990

Ser Ser Phe Ser Ala Asp Asn Leu Ala Ala Thr Asp Asp Asp Asn Glu 995 1000 1005

Met Asn Asn Leu Gln Ile Ala Val Asp Arg Met His Lys Gly Val 1010 1015

Ala Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe 1025 1030 1035

Ile Arg Lys Gln Lys Ile Leu Asp Glu Ile Lys Pro Leu Asp Asp 1040 1045 1050

Leu Asn Asn Lys Lys Asp Ser Cys Met Ser Asn His Thr Thr Glu 1055 1065

Ile Gly Lys Asp Leu Asp Tyr Leu Lys Asp Val Asn Gly Thr Thr 1070 1075 1080

Ser Gly Ile Gly Thr Gly Ser Ser Val Glu Lys Tyr Ile Ile Asp 1085 1090 1095

Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val 1100 1105 1110

Thr Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn 1115 1120 1125

Thr Glu Asp Phe Ser Ser Glu Ser Asp Leu Glu Glu Ser Lys Glu 1130 1140

Lys Leu Asn Glu Ser Ser Ser Ser Glu Gly Ser Thr Val Asp 1145 1150 1155

Ile Gly Ala Pro Val Glu Glu Gln Pro Val Val Glu Pro Glu Glu 1160 1170

Thr Leu Glu Pro Glu Ala Cys Phe Thr Glu Gly Cys Val Gln Arg 1175 1180 1185

Phe Lys Cys Cys Gln Ile Asn Val Glu Glu Gly Arg Gly Lys Gln 1190 1200

Trp Trp Asn Leu Arg Arg Thr Cys Phe Arg Ile Val Glu His Asn

Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu Leu Ser Ser Gly Page 128

PCT/AU2004/001051

SSCP Update Sequences.ST25 1220 1225 1230

Ala Leu Ala Phe Glu Asp Ile Tyr Ile Asp Gln Arg Lys Thr Ile 1235 1240 1245

Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr Ile Phe 1250 1260

Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Tyr Gln Thr 1265 1270 1275

Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp 1280 1285

Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr Ser Glu 1295 1300

Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro 1310 1315 1320

Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Val Val Asn 1325 1330 1335

Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val 1340 1350

Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu 1355 1360

Phe Ala Gly Lys Phe Tyr His Cys Ile Asn Thr Thr Gly Asp 1370 1380

Arg Phe Asp Ile Glu Asp Val Asn Asn His Thr Asp Cys Leu Lys 1385 1390 1395

Leu Ile Glu Arg Asn Glu Thr Ala Arg Trp Lys Asn Val Lys Val 1400 1405 1410

Asn Phe Asp Asn Val Gly Phe Gly Tyr Leu Ser Leu Leu Gln Val 1415 1420 1425

Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala Ala Val Asp 1430 1440

Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr Glu Lys Ser Leu Tyr 1445 1450 1455

Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe Phe 1460 1470

Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln Page 129

SSCP Update Sequences.ST25 1475 1480 1485

Gln Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu 1490 1495 1500 Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys 1505 1510 1515Pro Gln Lys Pro Ile Pro Arg Pro Gly Asn Lys Phe Gln Gly Met 1520 1530 Val Phe Asp Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met 1535 1540 1545 Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Ser Glu Tyr Val Thr Thr Ile Leu Ser Arg Ile Asn Leu 1565 1570 1575 Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser Leu Arg His Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Ile Leu Ser Ile Val Gly Met Phe Leu Ala Glu Leu Ile Glu Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala 1640 1650 Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met Met Ser Leu Pro 1655 1660 1665 Ala Leu Phe Asn Ile Gly Leu Leu Phe Leu Val Met Phe Ile 1670 1680 1680 Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly 1715 1720 1725 Leu Leu Ala Pro Ile Leu Asn Ser Lys Pro Pro Asp Cys Asp Pro

SSCP Update Sequences.ST25 1730 1735 1740

Asn Lys Val Asn Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn 1745 1750 1755 Pro Ser Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val Val Val Asn Met Tyr Ile Ala Val Ile Leu Glu Asn 1775 1780 1785 Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp 1790 1795 1800 Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Met Glu Phe Glu Lys Leu Ser Gln Phe Ala Ala Ala Leu Glu Pro Pro Leu Asn Leu Pro Gln Pro Asn Lys Leu Gln Leu Ile Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His 1850 1860 Cys Leu Asp Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Gln Pro Ile Thr Thr 1895 Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Val Ile Ile Gln Arg Ala Tyr Arg Arg His Leu Leu Lys Arg Thr Val Lys Gln Ala 1925 1930 1935 Ser Phe Thr Tyr Asn Lys Asn Lys Ile Lys Gly Gly Ala Asn Leu Leu Ile Lys Glu Asp Met Ile Ile Asp Arg Ile Asn Glu Asn Ser

Ile Thr Glu Lys Thr Asp Leu Thr Met Ser Thr Ala Ala Cys Pro

Pro Ser Tyr Asp Arg Val Thr Lys Pro Ile Val Glu Lys His Glu

Page 131

1970

SSCP Update Sequences.ST25 1985 1990 1995

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<210> 76

<211> 2009

<212> PRT

<213> Homo sapiens

<400> 76

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Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu 20 25 30

Lys Ala Lys Asn Pro Lys Pro Asp Lys Asp Asp Asp Glu Asn Gly 40 45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile 50 60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu 65 70 75 80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu 85 90 95

Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr  $100 \hspace{1cm} 105 \hspace{1cm} 110$ 

Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser 115 120 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe 130 140

Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr 145 150 155 160

Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg 165 170 175

Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp 180 185 190

Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp 195 200 205

Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu 210 215 220 Page 132

### SSCP Update Sequences.ST25

Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu 225 230 235 240 Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe 245 250 255 Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn 260 265 270 Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu 275 280 285 Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu 290 295 300 Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp 305 310 315 Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys 325 330 335 Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val 340 345 350 Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe 355 360 365 Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp 370 380 Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr Met 385 390 400 Ile Phe Leu Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Ile Asn 405 410 415Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala 420 425 430 Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met Ile 435 440 445 Glu Gln Leu Lys Lys Gln Gln Glu Ala Ala Gln Gln Ala Ala Thr Ala 450 455 460 Thr Ala Ser Glu His Ser Arg Glu Pro Ser Ala Ala Gly Arg Leu Ser 465 470 475 480 Asp Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala Lys Glu 485 490 495 Page 133

SSCP Update Sequences.ST25

Arg Arg Asn Arg Arg Lys Lys Arg Lys Gln Lys Glu Gln Ser Gly Gly 500 505 Glu Glu Lys Asp Glu Asp Glu Phe Gln Lys Ser Glu Ser Glu Asp Ser 515 520 525 Ile Arg Arg Lys Gly Phe Arg Phe Ser Ile Glu Gly Asn Arg Leu Thr 530 540 Tyr Glu Lys Arg Tyr Ser Ser Pro His Gln Ser Leu Leu Ser Ile Arg 545 550 555 560 Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Thr Ser Leu Phe Ser 565 570 575 Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp Phe Ala Asp 580 585 Asp Glu His Ser Thr Phe Glu Asp Asn Glu Ser Arg Asp Ser Leu 595 600 605 Phe Val Pro Arg Arg His Gly Glu Arg Arg Asn Ser Asn Leu Ser Gln 610 615 620 Thr Ser Arg Ser Ser Arg Met Leu Ala Val Phe Pro Ala Asn Gly Lys 625 630 635 Met His Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Val Gly Gly 645 650 655 Pro Ser Val Pro Thr Ser Pro Val Gly Gln Leu Leu Pro Glu Val Ile 660 665 670 Ile Asp Lys Pro Ala Thr Asp Asp Asn Gly Thr Thr Glu Thr Glu 685 Met Arg Lys Arg Arg Ser Ser Ser Phe His Val Ser Met Asp Phe Leu 690 695 700 Glu Asp Pro Ser Gln Arg Gln Arg Ala Met Ser Ile Ala Ser Ile Leu 705 710 715 720 Thr Asn Thr Val Glu Glu Leu Glu Glu Ser Arg Gln Lys Cys Pro Pro 725 730 735 Cys Trp Tyr Lys Phe Ser Asn Ile Phe Leu Ile Trp Asp Cys Ser Pro 740 745 750 Tyr Trp Leu Lys Val Lys His Val Val Asn Leu Val Val Met Asp Pro 755 760 765 Page 134

#### SSCP Update Sequences.ST25

Phe Val Asp Leu Ala Ile Thr Ile Cys Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr Asp His Phe Asn Asn Val Leu 785 790 795 800 Thr Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Phe 805 810 Leu Lys Ile Ile Ala Met Asp Pro Tyr Tyr Tyr Phe Gln Glu Gly Trp 820 825 830 Asn Ile Phe Asp Gly Phe Ile Val Thr Leu Ser Leu Val Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val Leu Arg Ser Phe Arg Leu Leu 850 855 860 Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Met Leu Ile 865 870 880 Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Asp Cys Val Cys Lys Ile Ala Ser Asp Cys Gln 915 925 Leu Pro Arg Trp His Met Asn Asp Phe Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met 945 950 955 960 Glu Val Ala Gly Gln Ala Met Cys Leu Thr Val Phe Met Met Val Met 965 970 975 Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu 980 985 990 Ser Ser Phe Ser Ala Asp Asn Leu Ala Ala Thr Asp Asp Asp Asn Glu 995 1000 1005 Met Asn Asn Leu Gln Ile Ala Val Asp Arg Met His Lys Gly Val Ala Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe 1025 1030 1035 1030 Page 135

# SSCP Update Sequences.ST25

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Leu	Asn 1055	Asn	Lys	Lys	Asp	Ser 1060	Cys	Met	Ser	Asn	ніs 1065	Thr	Thr	Glu
Ile	Gly 1070	Lys	Asp	Leu	Asp	Tyr 1075	Leu	Lys	Asp	Val	Asn 1080	Gly	Thr	Thr
Ser	Gly 1085	Ile	Gly	Thr	Gly	ser 1090	Ser	Val	Glu	Lys	Tyr 1095	Ile	Ile	Asp
Glu	ser 1100	Asp	Tyr	Met	Ser	Phe 1105	Ile	Asn	Asn	Pro	ser 1110	Leu	Thr	Val
Thr	Val 1115	Pro	Ile	Ala	Val	Gly 1120	Glu	Ser	Asp	Phe	Glu 1125	Asn	Leu	Asn
Thr	Glu 1130	Asp	Phe	Ser	Ser	Glu 1135	Ser	Asp	Leu	Glu	Glu 1140	Ser	Lys	Glu
Lys	Leu 1145	Asn	Glu	Ser	Ser -	ser 1150	Ser	Ser	Glu	Gly	ser 1155	Thr	٧a٦	Asp
Ile	G]y 1160	Ala	Pro	Val	Glu	Glu 1165	Gln	Pro	∨al	Val	Glu 1170	Pro	Glu	Glu
Thr	Leu 1175	Glu	Pro	Glu	Ala	Cys 1180	Phe	Thr	Glu	Gly	Cys 1185	Val	Gln	Arg
Phe	Lys 1190	Cys	Cys	Gln	Ile	Asn 1195	Val	Glu	Glu	Gly	Arg 1200	Gly	Lys	Gln
Trp	Trp 1205	Asn	Leu	Arg	Arg	Thr 1210	Cys	Phe	Arg	Ile	Val 1215	Glu	His	Asn
Trp	Phe 1220	Glu	Thr	Phe	Ile	Val 1225	Phe	Met	Ile	Leu	Leu 1230	Ser	Ser	Gly
Ala	Leu 1235	дÌа	Phe	Glu	Asp	Ile 1240	Tyr	Ile	Asp	Gln	Arg 1245	Lys	Thr	Ile
Lys	Thr 1250	Met	Leu	Glu	Tyr	Ala 1255	Asp	Lys	val	Phe	Thr 1260	Tyr	Ile	Phe
Ile	Leu 1265	Glu	Met	Leu	Leu	Lys 1270	Trp	Va]	Ala	Tyr	Gly 1275	Tyr	Gln	Thr
Tyr	Phe 1280	Thr	Asn	Ala	Trp	Cys 1285	Trp		Asp ige 1		Leu 1290	Ile	Val	Asp

SSCP Update Sequences.ST25

Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr Ser Glu 1295 1300 Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro 1310 1315 1320 Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Val Val Asn 1325 1330 Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val 1340 1345 1350 Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu 1355 1360 1365 Phe Ala Gly Lys Phe Tyr His Cys Ile Asn Thr Thr Gly Asp 1370 1375 1380 Arg Phe Asp Ile Glu Asp Val Asn Asn His Thr Asp Cys Leu Lys 1385 1390 Leu Ile Glu Arg Asn Glu Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Phe Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala Ala Val Asp 1430 1440 Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr Glu Lys Ser Leu Tyr 1445 1450 1455 Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln 1475 1480 Gln Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu 1490 1500 Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys 1505 1510 Pro Gln Lys Pro Ile Pro Arg Pro Gly Asn Lys Phe Gln Gly Met 1520 1530 Phe Asp Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Page 137

SSCP Update Sequences.ST25

Ile	Leu 1550	Ile	Cys	Leu	Asn	Met 1555	val	Thr	Met	Met	Val 1560	Glu	Thr	Asp
Asp	G]n 1565	ser	Glu	Tyr	٧a٦	Thr 1570	Thr	IJе	Leu	Ser	Arg 1575	Ile	Asn	Leu
۷al	Phe 1580	Ile	val	Leu	Phe	Thr 1585	GТу	Glu	Cys	Val	Leu 1590	Lys	Leu	Ile
Ser	Leu 1595	Arg	His	Tyr	Tyr	Phe 1600	Thr	Ile	Glу	Trp	Asn 1605	Ile	Phe	Asp
Phe	val 1610	٧a٦	٧a٦	Ile	Leu	Ser 1615	Ile	Val	GТу	Met	Phe 1620	Leu	Аlа	Glu
Leu	Ile 1625	Glu	Lys	Tyr	Phe	Val 1630	Ser	Pro	Thr	Leu	Phe 1635	Arg	٧a٦	Ile
Arg	Leu 1640	Ala	Arg	Ile	Gly	Arg 1645	Ile	Leu	Arg	Leu	Ile 1650	Lys	Gly	Ala
Lys	Gly 1655	Ile	Arg	Thr	Leu	Leu 1660	Phe	Ala	Leu	Met	Met 1665	Ser	Leu	Pro
Ala	Leu 1670	Phe	Asn	Ile	Gly	Leu 1675	Leu	Leu	Phe	Leu	Val 1680	Met	Phe	Ile
Tyr	Ala 1685	Ile	Phe	Glу	Met	Ser 1690	Asn	Phe	Аlа	Tyr	Val 1695	Lys	Arg	Glu
∨al	Gly 1700	Ile	Asp	Asp	Met	Phe 1705	Asn	Phe	Glu	Thr	Phe 1710	Gly	Asn	Ser
Met	Ile 1715	Cys	Leu	Phe	Gln	Ile 1720	Thr	Thr	ser	Ala	Gly 1725	Trp	Asp	Gly
Leu	Leu 1730	Ala	Pro	Ile	Leu	Asn 1735	Ser	Lys	Pro	Pro	Asp 1740	Cys	Asp	Pro
Asn	Lys 1745	val	Asn	Pro	Gly	Ser 1750	Ser	۷al	Lys	Gly	Asp 1755	Cys	Gly	Asn
Pro	ser 1760	val	Gly	Ile	Phe	Phe 1765	Phe	val	Ser	Tyr	Ile 1770	Ile	Ile	Ser
Phe	Leu 1775	val	٧a٦	٧a٦	Asn	Met 1780	Tyr	Ile	Аlа	val	Ile 1785	Leu	Glu	Asn
Phe	Ser 1790	val	Ala	Thr	Glu	Glu 1795	Ser		Glu age :		Leu 1800	Ser	Glu	Asp

SSCP Update Sequences.ST25

Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Met Glu Phe Glu Lys Leu Ser Gln Phe Ala Ala 1820 1825 1830 Ala Leu Glu Pro Pro Leu Asn Leu Pro Gln Pro Asn Lys Leu Gln Leu Ile Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His 1850 1860 Cys Leu Asp Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe 1880 1885 Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Gln Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Val Ile Ile Gln Arg Ala Tyr Arg Arg His Leu Leu Lys Arg Thr Val Lys Gln Ala 1925 1930 1935 Ser Phe Thr Tyr Asn Lys Asn Lys Ile Lys Gly Gly Ala Asn Leu 1940 1945 1950 Leu Ile Lys Glu Asp Met Ile Ile Asp Arg Ile Asn Glu Asn Ser 1955 1960 1965 Ile Thr Glu Lys Thr Asp Leu Thr Met Ser Thr Ala Ala Cys Pro Pro Ser Tyr Asp Arg Val Thr Lys Pro Ile Val Glu Lys His Glu 1995 1990 Gln Glu Gly Lys Asp Glu Lys Ala Lys Gly Lys 2000 2005 <210> 2009 <211> <212> PRT

Met Glu Gln Thr Val Leu Val Pro Pro Gly Pro Asp Ser Phe Asn Phe 1 10 15

<213> Homo sapiens

<400> 77

SSCP Update Sequences.ST25

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35 40 45 Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile 50 60 Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu 65 70 75 80 Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu 85 90 95 Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr  $100 \hspace{1cm} 105 \hspace{1cm} 110$ Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser 115 120 125 Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe 130 140 Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr 145 150 155 160Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg 165 170 175Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp 180 185 190 Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp 195 200 205 Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu 210 215 220 Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu 225 230 235 240 Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe 245 250 255 Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn 260 265 270 Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu 275 280 285

SSCP Update Sequences.ST25

Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu 290 295 300 Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp 305 310 315 320 Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys 325 330 335 Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val 340 345 350 Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe 355 360 365 Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp 370 375 380 Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr Met 385 390 395 400 Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Asn Leu Ile Asn 405 410 415Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala 420 425 430 Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met Ile 435 440 445 Glu Gln Leu Lys Lys Gln Gln Glu Ala Ala Gln Gln Ala Ala Thr Ala 450 455 460 Thr Ala Ser Glu His Ser Arg Glu Pro Ser Ala Ala Gly Arg Leu Ser 465 470 480 Asp Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala Lys Glu 485 490 495 Arg Arg Asn Arg Lys Lys Arg Lys Gln Lys Glu Gln Ser Gly Gly 500 505 Glu Glu Lys Asp Glu Asp Glu Phe Gln Lys Ser Glu Ser Glu Asp Ser 515 520 525 Ile Arg Arg Lys Gly Phe Arg Phe Ser Ile Glu Gly Asn Arg Leu Thr 530 535 540 Tyr Glu Lys Arg Tyr Ser Ser Pro His Gln Ser Leu Leu Ser Ile Arg 545 550 555

SSCP Update Sequences.ST25

Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Thr Ser Leu Phe Ser 565 570 575 Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp Phe Ala Asp 580 585 Asp Glu His Ser Thr Phe Glu Asp Asn Glu Ser Arg Asp Ser Leu 595 600 605 Phe Val Pro Arg Arg His Gly Glu Arg Arg Asn Ser Asn Leu Ser Gln 610 615 620 Thr Ser Arg Ser Ser Arg Met Leu Ala Val Phe Pro Ala Asn Gly Lys 625 630 635 Met His Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Val Gly Gly 645 650 655 Pro Ser Val Pro Thr Ser Pro Val Gly Gln Leu Leu Pro Glu Val Ile 660 665 670 Ile Asp Lys Pro Ala Thr Asp Asp Asn Gly Thr Thr Glu Thr Glu 675 680 685 Met Arg Lys Arg Arg Ser Ser Ser Phe His Val Ser Met Asp Phe Leu 690 700 Glu Asp Pro Ser Gln Arg Gln Arg Ala Met Ser Ile Ala Ser Ile Leu 705 710 715 720Thr Asn Thr Val Glu Glu Leu Glu Glu Ser Arg Gln Lys Cys Pro Pro 725 730 735 Cys Trp Tyr Lys Phe Ser Asn Ile Phe Leu Ile Trp Asp Cys Ser Pro
740 745 750 Tyr Trp Leu Lys Val Lys His Val Val Asn Leu Val Val Met Asp Pro 755 760 765 Phe Val Asp Leu Ala Ile Thr Ile Cys Ile Val Leu Asn Thr Leu Phe 770 780 Met Ala Met Glu His Tyr Pro Met Thr Asp His Phe Asn Asn Val Leu 785 790 795 800 Thr Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Phe 805 810 815 Leu Lys Ile Ile Ala Met Asp Pro Tyr Tyr Tyr Phe Gln Glu Gly Trp 820 825 830

SSCP Update Sequences.ST25

Asn Ile Phe Asp Gly Phe Ile Val Thr Leu Ser Leu Val Glu Leu Gly 835 840

Leu Ala Asn Val Glu Gly Leu Ser Val Leu Arg Ser Phe Arg Leu Leu 850 860

Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Met Leu Ile 865 870 875 880

Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val 885 890 895

Leu Ala Ile Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe 900 905 910

Gly Lys Ser Tyr Lys Asp Cys Val Cys Lys Ile Ala Ser Asp Cys Gln 915 920 925

Leu Pro Arg Trp His Met Asn Asp Phe Phe His Ser Phe Leu Ile Val 930 935 940

Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met 945 950 955 960

Glu Val Ala Gly Gln Ala Met Cys Leu Thr Val Phe Met Met Val Met 965 970 975

Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu 980 985 990

Ser Ser Phe Ser Ala Asp Asn Leu Ala Ala Thr Asp Asp Asp Asn Glu 995 1000 1005

Met Asn Asn Leu Gln Ile Ala Val Asp Arg Met His Lys Gly Val 1010 1020

Ala Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe 1025 1030 1035

Ile Arg Lys Gln Lys Ile Leu Asp Glu Ile Lys Pro Leu Asp Asp 1040 1050

Leu Asn Asn Lys Lys Asp Ser Cys Met Ser Asn His Thr Thr Glu 1055 1060

Ile Gly Lys Asp Leu Asp Tyr Leu Lys Asp Val Asn Gly Thr Thr 1070 1080

Ser Gly Ile Gly Thr Gly Ser Ser Val Glu Lys Tyr Ile Ile Asp 1085 1090 1095

SSCP Update Sequences.ST25

Glu	Ser 1100	Asp	Tyr	Met	Ser	Phe 1105	Ile	Asn	Asn	Pro	Ser 1110	Leu	Thr	val
Thr	∨a1 1115	Pro	Ile	Ala	۷al	Gly 1120	Glu	Ser	Asp	Phe	Glu 1125	Asn	Leu	Asn
Thr	Glu 1130	Asp,	Phe	Ser	Ser	Glu 1135	Ser	Asp	Leu	Glu	Glu 1140	Ser	Lys	Glu
Lys	Leu 1145	Asn	Glu	ser	Ser	Ser 1150	Ser	ser	Glu	Glу	ser 1155	Thr	Val	Asp
IJе	Gly 1160		Pro	va1	Glu	Glu 1165	Gln	Pro	٧al	Val	Glu 1170	Pro	Glu	Glu
Thr	Leu 1175		Pro	Glu	Ala	Cys 1180	Phe	Thr	Glu	Glу	Cys 1185	Val	Gln	Arg
Phe	Lys 1190		Cys	Gln	Ile	Asn 1195	٧a٦	Glu	Glu	GТу	Arg 1200	Glу	Lys	Gln
Trp	Trp 1205	Asn	Leu	Arg	Arg	Thr 1210	Cys	Phe	Arg	Ile	val 1215	Glu	His	Asn
Trp	Phe 1220	Glu	Thr	Phe	Ile	Val 1225	Phe	Met	Ile	Leu	Leu 1230	Ser	Ser	Gไу
Аlа	Leu 1235	Αla	Phe	Glu	Asp	Ile 1240	Tyr	Ile	Asp	Gln	Arg 1245	Lys	Thr	Ile
Lys	Thr 1250	Met	Leu	Glu	Tyr	Ala 1255	Asp	Lys	٧a٦	Phe	Thr 1260	Tyr	Ile	Phe
Ile	Leu 1265		Met	Leu	Leu	Lys 1270	Trp	Val	Аlа	Tyr	Gly 1275	Tyr	Gln	Thr
Tyr	Phe 1280	Thr	Asn	Αla	Тгр	Cys 1285	Trp	Leu	Asp	Phe	Leu 1290	Ile	Val	Asp
۷al	Ser 1295		۷a٦	Ser	Leu	Thr 1300		Asn	дlа	Leu	Gly 1305	Tyr	Ser	Glu
Leu	Gly 1310		Ile	Lys	Ser	Leu 1315	Arg	Thr	Leu	Arg	Ala 1320	Leu	Arg	Pro
Leu	Arg 1325		Leu	ser	Arg	Phe 1330	Glu	Gly	Met	Arg	Va7 1335	۷al	Val	Asn
Ala	Leu 1340		Glу	Ala	Ile	Pro 1345	Ser	Ile	Met	Asn	Va7 1350	Leu	Leu	Val

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SSCP Update Sequences.ST25

Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys Ile Asn Thr Thr Gly Asp 1370 1375 1380 Arg Phe Asp Ile Glu Asp Val Asn Asn His Thr Asp Cys Leu Lys Leu Ile Glu Arg Asn Glu Thr Ala Arg Trp Lys Asn Val Lys Val 1405 Asn Phe Asp Asn Val Gly Phe Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr Glu Lys Ser Leu Tyr 1445 1450 1455 Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe Phe 1460 1470 Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln Gln Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu 1490 1500 Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys 1505 1510 1515 Pro Gln Lys Pro Ile Pro Arg Pro Gly Asn Lys Phe Gln Gly Met 1520 1530 Val Phe Asp Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met 1535 1540 1545 Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr Asp Ser Glu Tyr Val Thr Thr Ile Leu Ser Arg 1570 Asp Gln Ile Asn Leu 1570 Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Val Phe 1585 1580 Ser Leu Arg His Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp

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							•		-	•				
Phe	val 1610	٧a٦	val	Ilе	Leu	ser 1615	Ile	٧al	Gly	Met	Phe 1620	Leu	Аlа	Glu
Leu	Ile 1625	Glu	Lys	Tyr	Phe	Va] 1630	Ser	Pro	Thr	Leu	Phe 1635	Arg	٧a٦	Ile
Arg	Leu 1640		Arg	Ile	Gly	Arg 1645	Ile	Leu	Arg	Leu	Ile 1650	Lys	Glу	Ala
Lys	Gly 1655	Ile	Arg	Thr	Leu	Leu 1660	Phe	Ala	Leu	Met	Met 1665	Ser	Leu	Pro
Ala	Leu 1670	Phe	Asn	Ile	Gly	Leu 1675	Leu	Leu	Phe	Leu	Val 1680	Met	Phe	Ile
Tyr	Ala 1685	Ile	Phe	Glу	Met	ser 1690	Asn	Phe	Αla	Tyr	Val 1695	Lys	Arg	Glu
۷al	Gly 1700		Asp	Asp	Met	Phe 1705	Asn	Phe	Glu	Thr	Phe 1710	Gly	Asn	Ser
Met	Ile 1715	Cys	Leu	Phe	Gln	Ile 1720	Thr	Thr	Ser	Ala	Gly 1725	Trp	Asp	Gly
Leu	Leu 1730	Ala	Pro	Ile	Leu	Asn 1735	Ser	Lys	Pro	Pro	Asp 1740	Cys	Asp	Pro
Asn	Lys 1745	val	Asn	Pro	Gly	Ser 1750	Ser	val	Lys	Gly	Asp 1755	Cys	Glу	Asn
Pro	ser 1760	val	Gly	Ile	Phe	Phe 1765	Phe	٧a٦	ser	Tyr	Ile 1770	Ile	Ile	Ser
Phe	Leu 1775	۷al	Val	٧a٦	Asn	Met 1780	Tyr	Ile	Ala	٧a٦	Ile 1785	Leu	Glu	Asn
Phe	Ser 1790	۷al	Аlа	Thr	Glu	Glu 1795	Ser	Ala	Glu	Pro	Leu 1800	Ser	Glu	Asp
Asp	Phe 1805	Glu	Met	Phe	Tyr	Glu 1810	٧a٦	Тгр	Glu	Lys	Phe 1815	Asp	Pro	Asp
Ala	Thr 1820	Gln	Phe	Met	Glu	Phe 1825	Glu	Lys	Leu	Ser	Gln 1830	Phe	Ala	Ala
Ala	Leu 1835	Glu	Pro	Pro	Leu	Asn 1840	Leu	Pro	Gln	Pro	Asn 1845	Lys	Leu	Gln
Leu	Ile 1850		Met	Asp	Leu	Pro 1855	Met	۷al	ser	Glу	Asp 1860	Arg	Ile	His
								Р	age	146				

SSCP Update Sequences.ST25

Cys Leu Asp Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu 1865 1875

Ser Gly Glu Met Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe 1880 1885 1890

Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Gln Pro Ile Thr Thr 1895 1900 1905

Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Val Ile Ile Gln 1910 1915 1920

Arg Ala Tyr Arg Arg His Leu Leu Lys Arg Thr Val Lys Gln Ala 1925 1930 1935

Ser Phe Thr Tyr Asn Lys Asn Lys Ile Lys Gly Gly Ala Asn Leu 1940 1945 1950

Leu Ile Lys Glu Asp Met Ile Ile Asp Arg Ile Asn Glu Asn Ser 1955 1960 1965

Ile Thr Glu Lys Thr Asp Leu Thr Met Ser Thr Ala Ala Cys Pro 1970 1980

Pro Ser Tyr Asp Arg Val Thr Lys Pro Ile Val Glu Lys His Glu 1985 1990 1995

Gln Glu Gly Lys Asp Glu Lys Ala Lys Gly Lys 2000 2005

<210> 78 <211> 2009

<211> 2009 <212> PRT

<213> Homo sapiens

<400> 78

Met Glu Gln Thr Val Leu Val Pro Pro Gly Pro Asp Ser Phe Asn Phe 1 10 15

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu 25 30

Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Asp Glu Asn Gly 35 40 45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile 50 60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu 65 70 75 80

SSCP Update Sequences.ST25 Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu 85 90 95 Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr  $100 \hspace{1cm} 105 \hspace{1cm} 110$ Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser 115 120 125 Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe 130 135 140 Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr 145 150 155 160Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg 165 170 175 Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp 180 185 190 Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp 195 200 205 Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu 210 220 Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu 225 230 235 240 Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe 245 250 255 Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn 260 265 270 Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu 275 280 285 Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu 290 295 300 Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp 305 310 315 320 Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys 325 330 335 Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val 340 345 350

SSCP Update Sequences.ST25
Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe 355 360 365 Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp 370 380 Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr Met 385 390 . 395 400 Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Ile Asn 405 410 415Leu Ile Leu Ala Val Glu Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala 420 425 430 Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met Ile 435 440 445 Glu Gln Leu Lys Lys Gln Gln Glu Ala Gln Gln Ala Ala Thr Ala 450 460 Thr Ala Ser Glu His Ser Arg Glu Pro Ser Ala Ala Gly Arg Leu Ser 465 470 475 480 Asp Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ála Lys Glu 485 490 495 Arg Arg Asn Arg Lys Lys Arg Lys Gln Lys Glu Gln Ser Gly Gly 500 505 Glu Glu Lys Asp Glu Asp Glu Phe Gln Lys Ser Glu Ser Glu Asp Ser 515 520 525 Ile Arg Arg Lys Gly Phe Arg Phe Ser Ile Glu Gly Asn Arg Leu Thr 530 540 Tyr Glu Lys Arg Tyr Ser Ser Pro His Gln Ser Leu Leu Ser Ile Arg 545 550 555 Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Thr Ser Leu Phe Ser 565 570 575 Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp Phe Ala Asp 580 585 Asp Glu His Ser Thr Phe Glu Asp Asn Glu Ser Arg Asp Ser Leu 595 605 Phe Val Pro Arg Arg His Gly Glu Arg Arg Asn Ser Asn Leu Ser Gln 610 620

SSCP Update Sequences.ST25
Thr Ser Arg Ser Ser Arg Met Leu Ala Val Phe Pro Ala Asn Gly Lys
625 630 635 640 Met His Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Val Gly Gly 645 650 655 Pro Ser Val Pro Thr Ser Pro Val Gly Gln Leu Leu Pro Glu Val Ile 660 670 Ile Asp Lys Pro Ala Thr Asp Asp Asn Gly Thr Thr Glu Thr Glu 675 680 685 Met Arg Lys Arg Arg Ser Ser Ser Phe His Val Ser Met Asp Phe Leu 690 695 700 Glu Asp Pro Ser Gln Arg Gln Arg Ala Met Ser Ile Ala Ser Ile Leu 705 710 715 720 Thr Asn Thr Val Glu Glu Leu Glu Glu Ser Arg Gln Lys Cys Pro Pro 725 730 735 Cys Trp Tyr Lys Phe Ser Asn Ile Phe Leu Ile Trp Asp Cys Ser Pro 740 745 750 Tyr Trp Leu Lys Val Lys His Val Val Asn Leu Val Val Met Asp Pro 755 760 765 Phe Val Asp Leu Ala Ile Thr Ile Cys Ile Val Leu Asn Thr Leu Phe 770 780 Met Ala Met Glu His Tyr Pro Met Thr Asp His Phe Asn Asn Val Leu 785 790 795 800 Thr Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Phe 805 810 815 Leu Lys Ile Ile Ala Met Asp Pro Tyr Tyr Tyr Phe Gln Glu Gly Trp 820 825 830 Asn Ile Phe Asp Gly Phe Ile Val Thr Leu Ser Leu Val Glu Leu Gly 835 840 845 Leu Ala Asn Val Glu Gly Leu Ser Val Leu Arg Ser Phe Arg Leu Leu 850 860 Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Met Leu Ile 865 870 875 880 Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val

SSCP Update Sequences.ST25 Leu Ala Ile Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe 900 905 910

- Gly Lys Ser Tyr Lys Asp Cys Val Cys Lys Ile Ala Ser Asp Cys Gln 915 920 925
- Leu Pro Arg Trp His Met Asn Asp Phe Phe His Ser Phe Leu Ile Val 930 935 940
- Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met 945 950 955 960
- Glu Val Ala Gly Gln Ala Met Cys Leu Thr Val Phe Met Met Val Met 965 970 975
- Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu 980 985 990
- Ser Ser Phe Ser Ala Asp Asn Leu Ala Ala Thr Asp Asp Asp Asn Glu 995 1000 1005
- Met Asn Asn Leu Gln Ile Ala Val Asp Arg Met His Lys Gly Val 1010 1015 1020
- Ala Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe 1025 1030 1035
- Ile Arg Lys Gln Lys Ile Leu Asp Glu Ile Lys Pro Leu Asp Asp 1040 1045 1050
- Leu Asn Asn Lys Lys Asp Ser Cys Met Ser Asn His Thr Thr Glu 1055 1060 1065
- Ile Gly Lys Asp Leu Asp Tyr Leu Lys Asp Val Asn Gly Thr Thr 1070 1075 1080
- Ser Gly Ile Gly Thr Gly Ser Ser Val Glu Lys Tyr Ile Ile Asp 1085 1090 1095
- Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val 1100 1105 1110
- Thr Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn 1115 1120 1125
- Thr Glu Asp Phe Ser Ser Glu Ser Asp Leu Glu Glu Ser Lys Glu 1130 1140
- Lys Leu Asn Glu Ser Ser Ser Ser Glu Gly Ser Thr Val Asp 1145 1150 1155

Ile	Gly 1160	Ala	Pro	∨al	Glu	SS6 Glu 1165	CP U _l Gln	odate Pro	e Sed Val	quen Val	ces.s ⁻ Glu 1170	T25 Pro	Glu	Glu
Thr	Leu 1175	Glu	Pro	Glu	Ala	Cys 1180	Phe	Thr	Glu	Gly	Cys 1185	∨al	Gln	Arg
Phe	Lys 1190	Cys	Cys	G∏n	Ile	Asn 1195	Val	Glu	Glu	Gly	Arg 1200	Gly	Lys	Gln
Trp	Trp 1205	Asn	Leu	Arg	Arg	Thr 1210	Cys	Phe	Arg	Ile	Val 1215	Glu	ніѕ	Asn
Trp	Phe 1220	Glu	Thr	Phe	Ile	Val 1225	Phe	Met	Ile	Leu	Leu 1230	Ser	Ser	Gly
Аlа	Leu 1235	Аlа	Phe	Glu	Asp	Ile 1240	Tyr	Ile	Asp	Gln	Arg 1245	Lys	Thr	Ile
Lys	Thr 1250	Met	Leu	Glu	Tyr	Ala 1255	Asp	Lys	∨al	Phe	Thr 1260	Tyr	Ile	Phe
Ile	Leu 1265	Glu	Met	Leu	Leu	Lys 1270	Trp	٧a٦	Ala	Tyr	Gly 1275	Tyr	Gln	Thr
Tyr	Phe 1280	Thr	Asn	Ala	Trp	Cys 1285	Trp	Leu	Asp	Phe	Leu 1290	Ile	٧a٦	Asp
٧a٦	Ser 1295	Leu	٧a٦	Ser	Leu	Thr 1300	Ala	Asn	Ala	Leu	Gly 1305	Tyr	Ser	Glu
Leu	Gly 1310		Ile	Lys	Ser	Leu 1315	Arg	Thr	Leu	Arg	Ala 1320	Leu	Arg	Pro
Leu	Arg 1325	Ala	Leu	Ser	Arg	Phe 1330	Glu	Gly	Met	Arg	Val 1335	Val	٧a٦	Asn
Ala	Leu 1340	Leu	Gly	Аlа	Ile	Pro 1345	ser	Ile	Met	Asn	Val 1350	Leu	Leu	Val
Cys	Leu 1355	Ile	Phe	Trp	Leu	Ile 1360	Phe	Ser	Ile	Met	Gly 1365	٧a٦	Asn	Leu
Phe	Ala 1370	Gly	Lys	Phe	Tyr	ніs 1375	Cys	Ile	Asn	Thr	Thr 1380	Thr	Gly	Asp
Arg	Phe 1385	Asp	Ile	Glu	Asp	Val 1390	Asn	Asn	His	Thr	Asp 1395	Cys	Leu	Lys
Leu	Ile 1400		Arg	Asn	Glu	Thr 1405	Ala	Arg	Trp	Lys	Asn 1410	∨al	Lys	Val

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Asn	Phe 1415	Asp	Asn	Val	Glу	550 Phe 1420	CP Up Gly	odate Tyr	e Seo Leu	quen Ser	ces.S ⁻ Leu 1425	Γ25 Leu	Gln	Val
Ala	Thr 1430	Phe	Lys	Glу	Trp	Меt 1435	Asp	Ile	Met	Tyr	А]а 1440	Ala	Val	Asp
ser	Arg 1445	Asn	väl	Glu	Leu	Gln 1450	Pro	Lys	Tyr	Glu	Lys 1455	Ser	Leu	Tyr
Met	Tyr 1460	Leu	Tyr	Phe	٧al	Ile 1465	Phe	Ile	Ile	Phe	Gly 1470	Ser	Phe	Phe
Thr	Leu 1475	Asn	Leu	Phe	Ile	Gly 1480	٧a٦	Ile	Ile	Asp	Asn 1485	Phe	Asn	Gln
Gln	Lys 1490	Lys	Lys	Phe	Gly	Gly 1495	Gln	Asp	Ile	Phe	Met 1500	Thr	Glu	Glu
Gln	Lys 1505	Lys	Tyr	Tyr	Asn	Ala 1510	Met	Lys	Lys	Leu	Gly 1515	Ser	Lys	Lys
Pro	Gln 1520	Lys	Pro	Ile	Pro	Arg 1525	Pro	Gly	Asn	Lys	Phe 1530	Gln	Gly	Met
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Ile	Leu 1550	Ile	Cys	Leu	Asn	Met 1555	val	Thr	Met	Met	va7 1560	Glu	Thr	Asp
Asp	Gln 1565	Ser	Glu	Tyr	٧a٦	Thr 1570	Thr	Ile	Leu	Ser	Arg 1575	Ile	Asn	Leu
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Leu	Ile 1625		Lys	Tyr	Phe	Val 1630	Ser	Pro	Thr	Leu	Phe 1635	Arg	Val	Ile
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Lys	Gly 1655		Arg	Thr	Leu	Leu 1660		Ala	Leu	Met	Met 1665	Ser	Leu	Pro

Ala	Leu 1670	Phe	Asn	Ile	Gly	SS Leu 1675	CP UI Leu	odate Leu	e Seo Phe	quen Leu	ces.s Val 1680	T25 Met	Phe	Ile
Tyr	Ala 1685	Ile	Phe	Glу	Met	ser 1690	Asn	Phe	Ala	Tyr	Val 1695	Lys	Arg	Glu
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Met	Ile 1715	Cys	Leu	Phe	Gln	Ile 1720	Thr	Thr	Ser	ΑΊа	Gly 1725	Trp	Asp	Gly
Ľeu	Leu 1730	Ala	Pro	Ile	Leu	Asn 1735	Ser	Lys	Pro	Pro	Asp 1740	Cys	Asp	Pro
Asn	Lys 1745	٧a٦	Asn	Pro	Gly	Ser 1750	Ser	val	Lys	Glу	Asp 1755	Cys	Gly	Asn
Pro	Ser 1760	val	Gly	Пe	Phe	Phe 1765	Phe	∨al	Ser	Tyr	Ile 1770	Ile	Ile	Ser
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Asp	Phe 1805	Glu	Met	Phe	Tyr	Glu 1810	٧a٦	Тгр	Glu	Lys	Phe 1815	Asp	Pro	Asp
Аlа	Thr 1820	Gln	Phe	Met	Glu	Phe 1825	Glu	Lys	Leu	Ser	Gln 1830	Phe	Ala	Ala
	Leu 1835									Pro	Asn 1845	Lys	Leu	Gln
Leu	Ile 1850	Ala	Met	Asp	Leu	Pro 1855	Met	Val	Ser	Gly	Asp 1860	Arg	Ile	His
Cys	Leu 1865	Asp	Ile	Leu	Phe	Ala 1870	Phe	Thr	Lys	Arg	Val 1875	Leu	GТу	Glu
Ser	Gly 1880	Glu	Met	Asp	Ala	Leu 1885	Arg	Ile	Gln	Met	Glu 1890	Glu	Arg	Phe
Met	Ala 1895	Ser	Asn	Pro	Ser	Lys 1900	val	Ser	Tyr	Gln	Pro 1905	Ile	Thr	Thr
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1925 1930 1935

Ser Phe Thr Tyr Asn Lys Asn Lys Ile Lys Gly Gly Ala Asn Leu 1940 1945 1950

Leu Ile Lys Glu Asp Met Ile Ile Asp Arg Ile Asn Glu Asn Ser 1955 1960 1965

Ile Thr Glu Lys Thr Asp Leu Thr Met Ser Thr Ala Ala Cys Pro 1970 1980

Pro Ser Tyr Asp Arg Val Thr Lys Pro Ile Val Glu Lys His Glu 1985 1990 1995

Gln Glu Gly Lys Asp Glu Lys Ala Lys Gly Lys 2000 2005

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Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Asp Glu Asn Gly 35 40 45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile 50 60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu 65 70 75 80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu 85 90 95

Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr 100 105 110

Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser 115 120 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe 130 140

Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr Page 155

SSCP Update Sequences.ST25 145 150 155 160

Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg 165 170 175

Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp 180 185 190

Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp 195 200 205

Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu 210 215 220

Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu 225 230 235 240

Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe 245 250

Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn 260 265 270

Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu 275 280 285

Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu 290 295 4 300

Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp 305 310 315 320

Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys 325 330 335

Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val 340 345 350

Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe 355 360 365

Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp 370 375 380

Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr Met 385 390 395 400

Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Ile Asn 405 410 415

Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala Page 156 SSCP Update Sequences.ST25 420 425 430 PCT/AU2004/001051

Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met Ile 435 440 445 Glu Gln Leu Lys Lys Gln Gln Glu Ala Gln Gln Ala Ala Thr Ala 450 460 Thr Ala Ser Glu His Ser Arg Glu Pro Ser Ala Ala Gly Arg Leu Ser 465 470 475 480 Asp Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala Lys Glu 485 490 495 Arg Arg Asn Arg Arg Lys Lys Arg Lys Gln Lys Glu Gln Ser Gly Gly 500 505 Glu Glu Lys Asp Glu Asp Glu Phe Gln Lys Ser Glu Ser Glu Asp Ser 515 520 525 Ile Arg Arg Lys Gly Phe Arg Phe Ser Ile Glu Gly Asn Arg Leu Thr 530 540 Tyr Glu Lys Arg Tyr Ser Ser Pro His Gln Ser Leu Leu Ser Ile Arg 545 550 555 Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Thr Ser Leu Phe Ser 565 570 575 Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp Phe Ala Asp 580 585 590 Asp Glu His Ser Thr Phe Glu Asp Asn Glu Ser Arg Arg Asp Ser Leu 595 600 605 Phe Val Pro Arg Arg His Gly Glu Arg Arg Asn Ser Asn Leu Ser Gln 610 615 Thr Ser Arg Ser Ser Arg Met Leu Ala Val Phe Pro Ala Asn Gly Lys 625 630 635 640 Met His Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Val Gly Gly 645 650 655 Pro Ser Val Pro Thr Ser Pro Val Gly Gln Leu Leu Pro Glu Val Ile 660 665 670 Ile Asp Lys Pro Ala Thr Asp Asp Asn Gly Thr Thr Glu Thr Glu 675 680 685 Met Arg Lys Arg Arg Ser Ser Ser Phe His Val Ser Met Asp Phe Leu Page 157

WO 2005/014863

690

SSCP Update Sequences.ST25 695 700 PCT/AU2004/001051

Glu Asp Pro Ser Gln Arg Gln Arg Ala Met Ser Ile Ala Ser Ile Leu 705 710 715 720 Thr Asn Thr Val Glu Glu Leu Glu Glu Ser Arg Gln Lys Cys Pro Pro 725 730 735 Cys Trp Tyr Lys Phe Ser Asn Ile Phe Leu Ile Trp Asp Cys Ser Pro 740 745 750 Tyr Trp Leu Lys Val Lys His Val Val Asn Leu Val Val Met Asp Pro 755 760 765 Phe Val Asp Leu Ala Ile Thr Ile Cys Ile Val Leu Asn Thr Leu Phe 770 780 Met Ala Met Glu His Tyr Pro Met Thr Asp His Phe Asn Asn Val Leu 785 790 795 800 Thr Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Phe 805 810 815 Leu Lys Ile Ile Ala Met Asp Pro Tyr Tyr Tyr Phe Gln Glu Gly Trp 820 825 830 Asn Ile Phe Asp Gly Phe Ile Val Thr Leu Ser Leu Val Glu Leu Gly 835 840 845 Leu Ala Asn Val Glu Gly Leu Ser Val Leu Arg Ser Phe Arg Leu Leu 850 860 Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Met Leu Ile 865 870 875 880 Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val 885 890 895 Leu Ala Ile Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe 900 905 910 Gly Lys Ser Tyr Lys Asp Cys Val Cys Lys Ile Ala Ser Asp Cys Gln 915 920 925 Leu Pro Arg Trp His Met Asn Asp Phe Phe His Ser Phe Leu Ile Val 930 940 Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met 945 950 955 960

Glu Val Ala Gly Gln Ala Met Cys Leu Thr Val Phe Met Met Val Met

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975

SSCP Update Sequences.ST25 965 970

Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu 980 985 990

Ser Ser Phe Ser Ala Asp Asn Leu Ala Ala Thr Asp Asp Asp Glu 995 1000 1005

Met Asn Asn Leu Gln Ile Ala Val Asp Arg Met His Lys Gly Val 1010 1020

Ala Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe 1025 1030 1035

Ile Arg Lys Gln Lys Ile Leu Asp Glu Ile Lys Pro Leu Asp Asp 1040 1045 1050

Leu Asn Asn Lys Lys Asp Ser Cys Met Ser Asn His Thr Thr Glu 1055 1065

Ile Gly Lys Asp Leu Asp Tyr Leu Lys Asp Val Asn Gly Thr Thr 1070 1080

Ser Gly Ile Gly Thr Gly Ser Ser Val Glu Lys Tyr Ile Ile Asp 1085 1090 1095

Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val 1100 1105 1110

Thr Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn 1115 1120 1125

Thr Glu Asp Phe Ser Ser Glu Ser Asp Leu Glu Glu Ser Lys Glu 1130 1140

Lys Leu Asn Glu Ser Ser Ser Ser Glu Gly Ser Thr Val Asp 1145 1150 1155

Ile Gly Ala Pro Val Glu Glu Gln Pro Val Val Glu Pro Glu Glu 1160 1170

Thr Leu Glu Pro Glu Ala Cys Phe Thr Glu Gly Cys Val Gln Arg 1175 1180 1185

Phe Lys Cys Cys Gln Ile Asn Val Glu Glu Gly Arg Gly Lys Gln 1190 1195 1200

Trp Trp Asn Leu Arg Arg Thr Cys Phe Arg Ile Val Glu His Asn 1205 1210 1215

Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu Leu Ser Ser Gly
Page 159

SSCP Update Sequences.ST25 1220 1225 1230

Ala Leu Ala Phe Glu Asp Ile Tyr Ile Asp Gln Arg Lys Thr Ile 1235 1240 1245

Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr Ile Phe 1250 1260

Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Tyr Gln Thr 1265 1270 1275

Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp 1280 1285 1290

Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr Ser Glu 1295 1300 1305

Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro 1310 1315 1320

Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Val Val Asn 1325 1330 1335

Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val 1340 1350

Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu 1355 1360 1365

Phe Ala Gly Lys Phe Tyr His Cys Ile Asn Thr Thr Thr Gly Asp 1370 1375 1380

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Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Glu Asn Gly
35 40 45
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## SSCP Update Sequences.ST25

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile 50 55 60 Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu 65 70 75 80 Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu 85 90 95 Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr  $100 \hspace{1cm} 105 \hspace{1cm} 110$ Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser 115 120 125 Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe 130 140 Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr 145 150 155 160 Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg 165 170 175 Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp 180 185 190 Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp 195 200 205 Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu 210 215 220 Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu 225 230 235 240 Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe 245 250 255 Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn 260 265 270 Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu 275 280 285 Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu 290 295 300 Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp 305 310 315 320 Page 161

## SSCP Update Sequences.ST25

Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys 325 330 335 Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val 340 345 350 Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe 355 360 365 Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp 370 375 380 Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr Met 385 390 395 400 Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Ile Asn  $405 \hspace{1.5cm} 410 \hspace{1.5cm} 415$ Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala 420 425 430 Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met Ile 435 440 445 Glu Gln Leu Lys Lys Gln Gln Glu Ala Ala Gln Gln Ala Ala Thr Ala 450 455 460 Thr Ala Ser Glu His Ser Arg Glu Pro Ser Ala Ala Gly Arg Leu Ser 465 470 475 480 Asp Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala Lys Glu
485 490 495 Arg Arg Asn Arg Arg Lys Lys Arg Lys Gln Lys Glu Gln Ser Gly Gly 500 510 Glu Glu Lys Asp Glu Asp Glu Phe Gln Lys Ser Glu Ser Glu Asp Ser 515 520 525 Ile Arg Arg Lys Gly Phe Arg Phe Ser Ile Glu Gly Asn Arg Leu Thr 530 540 Tyr Glu Lys Arg Tyr Ser Ser Pro His Gln Ser Leu Leu Ser Ile Arg 545 550 555 Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Thr Ser Leu Phe Ser 565 570 575 Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp Phe Ala Asp 580 585 590 Page 162

SSCP Update Sequences.ST25

Asp Glu His Ser Thr Phe Glu Asp Asn Glu Ser Arg Asp Ser Leu 595 600 605 Phe Val Pro Arg Arg His Gly Glu Arg Arg Asn Ser Asn Leu Ser Gln 610 615 620 Thr Ser Arg Ser Ser Arg Met Leu Ala Val Phe Pro Ala Asn Gly Lys 625 630 640 Met His Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Val Gly Gly 645 650 655 Pro Ser Val Pro Thr Ser Pro Val Gly Gln Leu Leu Pro Glu Val Ile 660 665 670 Ile Asp Lys Pro Ala Thr Asp Asp Asn Gly Thr Thr Glu Thr Glu 675 680 685 Met Arg Lys Arg Arg Ser Ser Ser Phe His Val Ser Met Asp Phe Leu 690 700 Glu Asp Pro Ser Gln Arg Gln Arg Ala Met Ser Ile Ala Ser Ile Leu 705 710 715 720 Thr Asn Thr Val Glu Glu Leu Glu Glu Ser Arg Gln Lys Cys Pro Pro
725 730 735 Cys Trp Tyr Lys Phe Ser Asn Ile Phe Leu Ile Trp Asp Cys Ser Pro 740 745 750 Tyr Trp Leu Lys Val Lys His Val Val Asn Leu Val Val Met Asp Pro 755 760 765 Phe Val Asp Leu Ala Ile Thr Ile Cys Ile Val Leu Asn Thr Leu Phe 770 780 Met Ala Met Glu His Tyr Pro Met Thr Asp His Phe Asn Asn Val Leu 785 790 795 800 Thr Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Phe 805 810 815 Leu Lys Ile Ile Ala Met Asp Pro Tyr Tyr Phe Gln Glu Gly Trp 820 825 830 Asn Ile Phe Asp Gly Phe Ile Val Thr Leu Ser Leu Val Glu Leu Gly 835 840 Leu Ala Asn Val Glu Gly Leu Ser Val Leu Arg Ser Phe Arg Leu Leu 850 855 860 Page 163

## SSCP Update Sequences.ST25

Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Met Leu Ile 865 870 875 880 Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe  $900 \hspace{1.5cm} 905 \hspace{1.5cm} 910$ Gly Lys Ser Tyr Lys Asp Cys Val Cys Lys Ile Ala Ser Asp Cys Gln 915 920 925 Leu Pro Arg Trp His Met Asn Asp Phe Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met 945 950 955 960 Glu Val Ala Gly Gln Ala Met Cys Leu Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ala Asp Asn Leu Ala Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Asp Arg Met His Lys Gly Val 1010 1015 1020 Ala Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe 1025 1035 Ile Arg Lys Gln Lys Ile Leu Asp Glu Ile Lys Pro Leu Asp Asp 1040 1050 Leu Asn Asn Lys Lys Asp Ser Cys Met Ser Asn His Thr Thr Glu 1055 1065 Ser Gly Ile Gly Thr Gly Ser Ser Val Glu Lys Tyr Ile Ile Asp 1085 1090 1095 Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn 1115 1120 1125

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Lys	Leu 1145	Asn	Glu	Ser	Ser	Ser 1150	Ser	Ser	Glu	GΊу	Ser 1155	Thr	٧a٦	Asp
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Phe	Lys 1190	Cys	Cys	Gln	Ile	Asn 1195	٧a٦	Glu	Glu	Glу	Arg 1200	Gly	Lys	Gln
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Trp	Phe 1220	Glu	Thr	Phe	Ile	Val 1225	Phe	Met	Ile	Leu	Leu 1230	Ser	Ser	Gly
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Lys	Thr 1250	Met	Leu	Glu	Tyr	Ala 1255	Asp	Lys	∨al	Phe	Thr 1260	Tyr	Ile	Phe
Ile	Leu 1265	Glu	Met	Leu	Leu	Lys 1270	Тгр	Val	Αla	Tyr	Gly 1275	Tyr	G∏n	Thr
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Leu	Arg 1325	Ala	Leu	Ser	Arg	Phe 1330	Glu	Gไу	Met	Arg	Va] 1335	Val	Val	Asn
Ala	Leu 1340	Leu	Gly	Ala	Ile	Pro 1345	Ser	Ile	Met	Asn	Val 1350	Leu	Leu	٧a٦
Cys	Leu 1355	Ile	Phe	Trp	Leu	Ile 1360	Phe	Ser	Ile	Met	Gly 1365	Val	Asn	Leu
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Arg	Phe 1385	Asp	Ile	Glu	Asp	Val 1390	Asn	Asn	ніѕ	Thr	Asp 1395	Cys	Leu	Lys
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Ala	Thr 1430		Lys	Glу	Trp	Met 1435	Asp	Ile	Met	Tyr	А]а 1440	Ala	Val	Asp
Ser	Arg 1445	Asn	val	Glu	Leu	Gln 1450	Pro	Lys	Tyr	Glu	Lys 1455	Ser	Leu	Tyr
Met	Tyr 1460	Leu	Tyr	Phe	val	Ile 1465	Phe	Ile	Ile	Phe	Gly 1470	Ser	Phe	Phe
Thr	Leu 1475	Asn	Leu	Phe	Ile	Gly 1480	Val	Ile	ıle	Asp	Asn 1485	Phe	Asn	G]n
Gln	Lys 1490	Lys	Lys	Phe	Gly	Gly 1495	Gln	Asp	Ile	Phe	Met 1500	Thr	Glu	Glu
Gln	Lys 1505	Lys	Tyr	Tyr	Asn	Ala 1510	Met	Lys	Lys	Leu	Gly 1515	Ser	Lys	Lys
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Ile	Leu 1550		Cys	Leu	Asn	Met 1555	٧a٦	Thr	Met	Met	∨a1 1560	Glu	Thr	Asp
Asp	Gln 1565	Ser	Glu	Tyr	۷al	Thr 1570	Thr	Ile	Leu	Ser	Arg 1575 _,	Ile	Asn	Leu
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Ser	Leu 1595	Arg	His	Tyr	Tyr	Phe 1600	Thr	Ile	GТу	Trp	Asn 1605	Ile	. Phe	Asp
Phe	Val 1610		Val	Ile	Leu	ser 1615	Ile	۷a٦	GТу	Met	Phe 1620	Leu	Ala	Glu
Leu	Ile 1625	Glu	Lys	Tyr	Phe	Val 1630	Ser		Thr age		Phe 1635	Arg	val	Ile

Arg	Leu 1640	Αla	Arg	Ile	Glу	Arg 1645	Ile	Leu	Arg	Leu	Ile 1650	Lys	Gly	Аlа
Lys	Gly 1655	Ile	Arg	Thr	Leu	Leu 1660	Phe	Ala	Leu	Met	Met 1665	Ser	Leu	Pro
Ala	Leu 1670	Phe	Asn	Ile	Gly	Leu 1675	Leu	Leu	Phe	Leu	Val 1680	Met	Phe	Ile
Tyr	Ala 1685	Ile	Phe	Gly	Met	Ser 1690	Asn	Phe	Ala	Tyr	Val 1695	Lys	Arg	Glu
٧a٦	Gly 1700	Ile	Asp	Asp	Met	Phe 1705	Asn	Phe	Glu	Thr	Phe 1710	Gly	Asn	Ser
Met	Ile 1715	Cys	Leu	Phe	Gln	Ile 1720	Thr	Thr	ser	Аlа	Gly 1725	Trp	Asp	Gly
Leu	Leu 1730	Ala	Pro	ıle	Leu	Asn 1735	Ser	Lys	Pro	Pro	Asp 1740	Cys	Asp	Pro
Asn	Lys 1745	٧a٦	Asn	Pro	Gly	Ser 1750	Ser	٧a٦	Lys	Gly	Asp 1755	Cys	Glу	Asn
Pro	ser 1760	٧a٦	Gly	Ile	Phe	Phe 1765	Phe	Val	Ser	Tyr	Ile 1770	Ile	Ile	Ser
Phe	Leu 1775	٧a٦	٧a٦	٧a٦	Asn	Thr 1780	Tyr	Ile	Ala	Val	Ile 1785	Leu	Glu	Asn
Phe	Ser 1790	val	Аlа	Thr	Glu	Glu 1795	Ser	Ala	Glu	Pro	Leu 1800	Ser	Glu	Asp
Asp	Phe 1805	Glu	Met	Phe	Tyr	Glu 1810	Val	Trp	Glu	Lys	Phe 1815	Asp	Pro	Asp
Ala	Thr 1820	Gln	Phe	Met	Glu	Phe 1825	Glu	Lys	Leu	Ser	Gln 1830	Phe	Ala	Ala
Ala	Leu 1835	Glu	Pro	Pro	Leu	Asn 1840	Leu	Pro	Gln	Pro	Asn 1845	Lys	Leu	Gln
Leu	Ile 1850	Аla	Met	Asp	Leu	Pro 1855	Met	٧a٦	ser	Gly	Asp 1860	Arg	Ile	His
Cys	Leu 1865	Asp	Ile	Leu	Phe	Ala 1870	Phe	Thr	Lys	Arg	Val 1875	Leu	Gly	Glu
Ser	Gly 1880		Met	Asp	Ala	Leu 1885	Arg		Gln age		Glu 1890	Glu	Arg	Phe

## SSCP Update Sequences.ST25

Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Gln Pro Ile Thr Thr 1895 1900 1905

Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Val Ile Ile Gln 1910 1915 1920

Arg Ala Tyr Arg Arg His Leu Leu Lys Arg Thr Val Lys Gln Ala 1925 1930 1935

Ser Phe Thr Tyr Asn Lys Asn Lys Ile Lys Gly Gly Ala Asn Leu 1940 1945 1950

Leu Ile Lys Glu Asp Met Ile Ile Asp Arg Ile Asn Glu Asn Ser 1955 1960 1965

Ile Thr Glu Lys Thr Asp Leu Thr Met Ser Thr Ala Ala Cys Pro 1970 1975 1980

Pro Ser Tyr Asp Arg Val Thr Lys Pro Ile Val Glu Lys His Glu 1985 1990 1995

Gln Glu Gly Lys Asp Glu Lys Ala Lys Gly Lys 2000 2005

<210> 81

<211> 1891

<212> PRT

<213> Homo sapiens

<400> 81

Met Glu Gln Thr Val Leu Val Pro Pro Gly Pro Asp Ser Phe Asn Phe  $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ 

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu 20 25 30

Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Glu Asn Gly 40 45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile 50 60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu 65 70 75 80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Leu 85 90 95

Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr  $100 \hspace{1cm} 105 \hspace{1cm} 110$ 

SSCP Update Sequences.ST25

Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser . 115 120 125 Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe 130 140 Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr 145 150 155 160 Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg 165 170 175 Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp 180 185 190 Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp 195 200 205 Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu 210 220 Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu 225 230 235 240 Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe 245 250 255 Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn 260 265 270 Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu 275 280 285 Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu 290 295 300 Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp 305 310 315 Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys 325 330 335 Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val 340 345 350 Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe 355 360 365 Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp 370 380

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SSCP Update Sequences.ST25

Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr Met 385 390 395 400 Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Ile Asn 405 410 415 Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala 420 425 430 Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met Ile 435 440 445 Glu Gln Leu Lys Lys Gln Gln Glu Ala Ala Gln Gln Ala Ala Thr Ala 450 455 460 Thr Ala Ser Glu His Ser Arg Glu Pro Ser Ala Ala Gly Arg Leu Ser 465 470 475 480 Asp Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala Lys Glu 485 490 495 Arg Arg Asn Arg Lys Lys Arg Lys Gln Lys Glu Gln Ser Gly Gly 500 505 Glu Glu Lys Asp Glu Asp Glu Phe Gln Lys Ser Glu Ser Glu Asp Ser 515 520 525 Ile Arg Arg Lys Gly Phe Arg Phe Ser Ile Glu Gly Asn Arg Leu Thr 530 540 Tyr Glu Lys Arg Tyr Ser Ser Pro His Gln Ser Leu Leu Ser Ile Arg 545 550 555 560 Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Thr Ser Leu Phe Ser 575 Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp Phe Ala Asp 580 585 Asp Glu His Ser Thr Phe Glu Asp Asn Glu Ser Arg Asp Ser Leu 595 600 605 Phe Val Pro Arg Arg His Gly Glu Arg Arg Asn Ser Asn Leu Ser Gln 610 615 620 Thr Ser Arg Ser Ser Arg Met Leu Ala Val Phe Pro Ala Asn Gly Lys 625 630 635 640 Met His Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Val Gly Gly 645 650 655

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SSCP Update Sequences.ST25

Pro Ser Val Pro Thr Ser Pro Val Gly Gln Leu Leu Pro Glu Val Ile 660 665 670

Ile Asp Lys Pro Ala Thr Asp Asp Asn Gly Thr Thr Glu Thr Glu 675 680 685

Met Arg Lys Arg Arg Ser Ser Ser Phe His Val Ser Met Asp Phe Leu 690 700

Glu Asp Pro Ser Gln Arg Gln Arg Ala Met Ser Ile Ala Ser Ile Leu 705 710 715

Thr Asn Thr Val Glu Glu Leu Glu Glu Ser Arg Gln Lys Cys Pro Pro 725 730 735

Cys Trp Tyr Lys Phe Ser Asn Ile Phe Leu Ile Trp Asp Cys Ser Pro
740 745 750

Tyr Trp Leu Lys Val Lys His Val Val Asn Leu Val Val Met Asp Pro 755 760 765

Phe Val Asp Leu Ala Ile Thr Ile Cys Ile Val Leu Asn Thr Leu Phe 770 775 780

Met Ala Met Glu His Tyr Pro Met Thr Asp His Phe Asn Asn Val Leu 785 790 795 800

Thr Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Phe 805 810 815

Leu Lys Ile Ile Ala Met Asp Pro Tyr Tyr Tyr Phe Gln Glu Gly Trp 820 825 830

Asn Ile Phe Asp Gly Phe Ile Val Thr Leu Ser Leu Val Glu Leu Gly 835 840 845

Leu Ala Asn Val Glu Gly Leu Ser Val Leu Arg Ser Phe Arg Leu Leu 850 860

Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Met Leu Ile 865 870 875 880

Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val 885 890 895

Leu Ala Ile Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe 900 905 910

Gly Lys Ser Tyr Lys Asp Cys Val Cys Lys Ile Ala Ser Asp Cys Gln 915 920 925

SSCP Update Sequences.ST25

Leu Pro Arg Trp His Met Asn Asp Phe Phe His Ser Phe Leu Ile Val 930 935 940

Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met 945 950 955 960

Glu Val Ala Gly Gln Ala Met Cys Leu Thr Val Phe Met Met Val Met 965 970 975

Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu 980 985 990

Ser Ser Phe Ser Ala Asp Asn Leu Ala Ala Thr Asp Asp Asp Asn Glu 995 1000 1005

Met Asn Asn Leu Gln Ile Ala Val Asp Arg Met His Lys Gly Val 1010 1015 1020

Ala Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe 1025 1030 1035

Ile Arg Lys Gln Lys Ile Leu Asp Glu Ile Lys Pro Leu Asp Asp 1040 1045 1050

Leu Asn Asn Lys Lys Asp Ser Cys Met Ser Asn His Thr Thr Glu 1055 1060 1065

Ile Gly Lys Asp Leu Asp Tyr Leu Lys Asp Val Asn Gly Thr Thr 1070 1080

Ser Gly Ile Gly Thr Gly Ser Ser Val Glu Lys Tyr Ile Ile Asp 1085 1090 1095

Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val 1100 1105 1110

Thr Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn 1115 1120 1125

Thr Glu Asp Phe Ser Ser Glu Ser Asp Leu Glu Glu Ser Lys Glu 1130 1140

Lys Leu Asn Glu Ser Ser Ser Ser Glu Gly Ser Thr Val Asp 1145 1150

Ile Gly Ala Pro Val Glu Glu Fro Val Val Glu Pro Glu Glu 1160 1165 1170

Thr Leu Glu Pro Glu Ala Cys Phe Thr Glu Gly Cys Val Gln Arg 1175 1180 1185

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SSCP Update Sequences.ST25

Phe Lys Cys Cys Gln Ile Asn Val Glu Glu Gly Arg Gly Lys Gln 1190 1195 1200 Trp Trp Asn Leu Arg Arg Thr Cys Phe Arg Ile Val Glu His Asn 1205 1210 1215 Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Asp Gln Arg Lys Thr Ile 1235 1240 1245 Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr Ile Phe 1250 1260 Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Tyr Gln Thr 1265 1270 1275 Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp 1280 1285 1290 Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr Ser Glu 1295 1300 1305 Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro 1310 1315 1320 Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Val Val Asn 1325 1330 Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val 1340 1345 1350 Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys Ile Asn Thr Thr Gly Asp 1370 1375 1380 Arg Phe Asp Ile Glu Asp Val Asn Asn His Thr Asp Cys Leu Lys 1385 1390 1395 Leu Ile Glu Arg Asn Glu Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Phe Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala Ala Val Asp 1430 1435

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SSCP Update Sequences.ST25

Asn Val Glu Leu Gln Pro Lys Tyr Glu Lys Ser Leu Tyr 1450 1455 Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe Phe 1460 1465 1470Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln Gln Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu 1490 1500 Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys 1505 1510 1515 Pro Gln Lys Pro Ile Pro Arg Pro Gly Asn Lys Phe Gln Gly Met 1520 1530 Val Phe Asp Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met 1535 1540 1545 Asp Gln Ser Glu Tyr Val Thr Thr Ile Leu Ser Arg Ile Asn Leu 1565 1570 1575 Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser Leu Arg His Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Ile Leu Ser Ile Val Gly Met Phe Leu Ala Glu 1610 Leu Ile Glu Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Phe Leu Val Met Phe Ile 1680 1670 Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys Arg Glu

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<212> PRT

<213> Homo sapiens

<400> 82

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Ala Cys Gly Gly Cys Val Glu Val Asp Ser Glu Thr Glu Ala Val Tyr 20 25 30

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Thr Asn Ala Glu Thr Phe Thr Glu Trp Thr Phe Arg Gln Lys Gly Thr 50 55 60

Glu Glu Phe Val Lys Ile Leu Arg Tyr Glu Asn Glu Val Leu Gln Leu 65 70 75 80

Glu Glu Asp Glu His Phe Glu Gly Arg Val Val Trp Asn Gly Ser Arg . 85 90 95

Gly Thr Lys Asp Leu Gln Asp Leu Ser Ile Phe Ile Thr Asn Val Thr  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110$ 

Tyr Asn His Ser Gly Asp Tyr Glu Cys His Val Tyr Arg Leu Leu Phe 115 120 125

Phe Glu Asn Tyr Glu His Asn Thr Ser Val Val Lys Lys Ile His Ile 130 135 140

Glu Val Val Asp Lys Ala Asn Arg Asp Met Ala Ser Ile Val Ser Glu 145 150 155 160

Ile Met Met Tyr Val Leu Ile Val Val Leu Thr Ile Trp Leu Val Ala 165 170 175

Glu Met Ile Tyr Cys Tyr Lys Lys Ile Ala Ala Ala Thr Glu Thr Ala 180 185

Ala Gln Glu Asn Ala Ser Glu Tyr Leu Ala Ile Thr Ser Glu Ser Lys 195 200 205

Glu Asn Cys Thr Gly Val Gln Val Ala Glu 210 215

Met Ala Gln Ser Val Leu Val Pro Pro Gly Pro Asp Ser Phe Arg Phe 1 5 10 15

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Gln Arg Ile Ala Glu Glu 20 25 30

Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Glu Asn 35 40 45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe Page 176

<210> 83

<211> <212> 2005

PRT

<213> Homo sapiens

<400> 83

50

WO 2005/014863 PCT/AU2004/001051

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90
95 Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu  $100 \hspace{1cm} 105 \hspace{1cm} 110$ Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His 115 120 125 Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val 130 135 140 Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr 145 150 155 160 Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala 165 170 175 Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn 180 185 190 Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val 195 200 Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Gln Ala 210 215 220 Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala 225 230 235 240 Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val 245 250 255 Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly 260 265 270 Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe 275 280 285

Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile 305 310 315 320

Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly 290 295 300

Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu Page 177

335

SSCP Update Sequences.ST25 330

Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile 340 345 350 Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp 355 360 365 Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp 370 380 Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr 385 390 395 400 Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu 405 410 415Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn 420 425 430 Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln 435 440 445 Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala 450 455 460 Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile 465 470 475 480 Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys 485 490 495 Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Gln Lys Glu 500 505 Gln Ser Gly Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser 515 520 525 Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser 530 540 Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu 545 550 555 Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser 575 Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp 580 585 Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg Page 178

SSCP Update Sequences.ST25 600 605

595

Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn 610 620 Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met 625 630 640 Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu 645 650 655 Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu 660 665 670 Gly Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Tyr 675 680 685 His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala 690 695 700 Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu 705 710 715 720 Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys 725 730 735 Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val 740 745 750 Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys 755 760 765 Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr 770 780 Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly 785 790 795 800 Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr 805 810 815Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser 820 825 830 Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val 835 840 845 Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp 850 860 Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala Page 179

880

SSCP Update Sequences.ST25 870 875

865

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala 885 890 895

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys 900 905 910

Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe 915 920 925

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile 930 935 940

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu 945 950 955 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn 965 970 975

Leu Phe Leu Ala Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala 980 985 990

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly 995 1000 1005

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu 1010 1015 1020

Phe Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu 1025 1030 1035

Ile Lys Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile 1040 1045 1050

Ser Asn His Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu 1055 1060 1065

Lys Asp Gly Asn Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu 1070 1080

Lys Tyr Val Val Asp Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn 1085 1095

Pro Ser Leu Thr Val Thr Val Pro Ile Ala Val Gly Glu Ser Asp 1100 1105 1110

Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser Ser Glu Ser Asp Met 1115 1120 1125

Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser Ser Glu Gly Page 180

SSCP Update Sequences.ST25 1130 - 1135 1140

Ser Thr Val Asp Ile Gly Ala Pro Ala Glu Gly Glu Gln Pro Glu 1145 1150 1155

Val Glu Pro Glu Glu Ser Leu Glu Pro Glu Ala Cys Phe Thr Glu 1160 1165 1170

Asp Cys Val Arg Lys Phe Lys Cys Gln Ile Ser Ile Glu Glu 1175 1180 1185

Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr Cys Tyr Lys 1190 1200

Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile 1205 1210 1215

Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Glu 1220 1230

Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val 1235 1240 1245

Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala 1250 1260

Tyr Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp 1265 1270 1275

Phe Leu Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala 1280 1285 1290

Leu Gly Tyr Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu 1295 1300 1305

Arg Ala Leu Arg Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met 1310 1320

Arg Val Val Asn Ala Leu Leu Gly Ala Ile Pro Ser Ile Met 1325 1330 1335

Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile 1340 1345 1350

Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys Ile Asn 1355 1360 1365

Tyr Thr Thr Gly Glu Met Phe Asp Val Ser Val Val Asn Asn Tyr 1370 1380

Ser Glu Cys Lys Ala Leu Ile Glu Ser Asn Gln Thr Ala Arg Trp Page 181 SSCP Update Sequences.ST25 1385 1390 1395

Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Leu Gly Tyr Leu 1400 1405 1410

Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met 1415 1420 1425

Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr 1430 1440

Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile 1445 1450 1455

Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile 1460 1465 1470

Asp Asn Phe Asn Gln Gln Lys Lys Phe Gly Gln Asp Ile 1475 1480 1485

Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys 1490 1500

Leu Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn 1505 1515

Lys Phe Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe 1520 1530

Asp Ile Ser Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met 1535 1540 1545

Met Val Glu Thr Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu 1550 1560

Tyr Trp Ile Asn Leu Val Phe Ile Val Leu Phe Thr Gly Glu Cys 1565 1570 1575

Val Leu Lys Leu Ile Ser Leu Arg Tyr Tyr Phe Thr Ile Gly 1580 1585 1590

Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile Val Gly 1595 1600

Met Phe Leu Ala Glu Leu Ile Glu Lys Tyr Phe Val Ser Pro Thr 1610 1620

Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg 1625 1630 1635

Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Page 182 SSCP Update Sequences.ST25 1640 1645 1650

Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala 1670 1680 Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn Phe Glu 1685 1690 1695 Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser 1700 1705 Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro 1715 Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys 1730 1740 Gly Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Val Ser 1745 1750 Tyr Ile Ile Ile Ser Phe Leu Val Val Leu Asn Met Tyr Ile Ala 1765 Val Ile Leu Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala Leu Asp Pro Pro Leu Leu Ile Ala Lys 1820 1830 Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met Val Ser

Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln 1865 1870 1875

Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr Lys

Met Glu Glu Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr 1880 1890

Glu Pro Ile Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Page 183

SSCP Update Sequences.ST25 1895 1900 1905

Ala Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu Leu Lys Gln 1910 1915 1920

Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys Gly Lys 1925 1930 1935

Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp Lys 1940 1950

Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser 1955 1960 1965

Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys 1970 1980

Glu Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys 1985 1990 1995

Asp Ile Arg Glu Ser Lys Lys 2000

<210> 84

<211> 2005

<212> PRT

<213> Homo sapiens

<400> 84

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Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Gln Arg Ile Ala Glu Glu 20 25 30

Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Glu Asn 35 40 45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe 50 60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp 65 70 75 80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys 85 90 95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu 100 105 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His
115 120 125
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## SSCP Update Sequences.ST25

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val 130 140 Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr 145 150 155 160 Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala 165 170 175 Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn 180 185 Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val 195 200 205 Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala 210 215 220 Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala 225 230 235 240 Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val 245 250 255 Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly 260 265 270 Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe 275 280 285 Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly 290 295 300 Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile 305 310 315 320 Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu 325 330 335 Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile  $340 \hspace{1cm} 345 \hspace{1cm} 350$ Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp 355 360 365 Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp 370 380Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr 385 390 395 400 Page 185

SSCP Update Sequences.ST25

Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu 405 410 415Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn 420 425 430 Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln 445 445 Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala 450 455 460 Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile 465 470 480 Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys 485 490 495 Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Gln Lys Glu 500 510 Gln Ser Gly Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser 515 520 525 Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser 530 540 Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu 545 550 555 560 Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser 575 Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp 580 585 Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg 595 600 605 Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn 610 615 620 Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met 625 630 635 640 Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu 645 650 655 Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu 660 665 670 Page 186

SSCP Update Sequences.ST25

Gly Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Tyr 675 680 685 His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala 690 695 700 Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu 705 710 715Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys 725 730 735 Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val 740 745 750 Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys 755 760 765 Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr 770 780 Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly 785 790 795 800 Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr 805 810 815Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser 820 825 830 Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val 835 840 845 Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp 850 860 Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala 865 870 880 Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Ile Phe Ile Phe Ala 885 890 895 Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys 900 905 910 Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe 915 920 925 Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile 930 935 940 Page 187

## SSCP Update Sequences.ST25

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu 945 950 955 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn 965 970 975

Leu Phe Leu Ala Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala 980 985 990

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly 995 1000

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu 1010 1015 1020

Phe Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu 1025 1030 1035

Ile Lys Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile 1040 1045 1050

Ser Asn His Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu 1055 1065

Lys Asp Gly Asn Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu 1070 1080

Lys Tyr Val Val Asp Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn 1085 1095

Pro Ser Leu Thr Val Thr Val Pro Ile Ala Val Gly Glu Ser Asp 1100 1105 1110

Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser Ser Glu Ser Asp Met 1115 1120 1125

Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser Ser Glu Gly 1130 1140

Ser Thr Val Asp Ile Gly Ala Pro Ala Glu Gly Glu Gln Pro Glu 1145 1150

Val Glu Pro Glu Glu Ser Leu Glu Pro Glu Ala Cys Phe Thr Glu 1160 1165 1170

Asp Cys Val Arg Lys Phe Lys Cys Gln Ile Ser Ile Glu Glu 1175 1180 1185

Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr Cys Tyr Lys 1190 1195 1200 Page 188

## SSCP Update Sequences.ST25

Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile 1205 1210 1215 Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Glu 1220 1230 Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val 1235 1240 1245 Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Lys Trp Val Ala 1250 1255 1260 Tyr Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp 1265 1270 1275 Phe Leu Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu 1295 1300 Arg Ala Leu Arg Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met 1310 1320 Arg Val Val Asn Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile 1340 1345 Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys Ile Asn 1355 1360 1365 Tyr Thr Thr Gly Glu Met Phe Asp Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser Asn Gln Thr Ala Arg Trp 1385 1390 1395 Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr 1430 1440 Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Page 189

SSCP Update Sequences.ST25

Phe	Gly 1460	Ser	Phe	Phe	Thr	Leu 1465	Asn	Leu	Phe	Ile	Glу 1470	Val	Ile	Ile
Asp	Asn 1475	Phe	Asn	Gln	Gln	Lys 1480	Lys	Lys	Phe	Gly	Gly 1485	Gln	Asp	Ile
Phe	Met 1490	Thr	Glu	Glu	Gln	Lys 1495	Lys	Tyr	Tyr	Asn	Ala 1500	Met	Lys	Lys
Leu	Gly 1505	Ser	Lys	Lys	Pro	G]n 1510	Lys	Pro	Ile	Pro	Arg 1515	Pro	Ala	Asn
Lys	Phe 1520	Gln	Gly	Met	٧a٦	Phe 1525	Asp	Phe	٧a٦	Thr	Lys 1530	Gln	٧a٦	Phe
Asp	Ile 1535	Ser	Ile	Met	Ile	Leu 1540	Ile	Cys	Leu	Asn	Met 1545	Val	Thr	Met
Met	Val 1550	Glu	Thr	Asp	Asp	G]n 1555	Ser	Gln	Glu	Met	Thr 1560	Asn	Ile	Leu
Tyr	Trp 1565	Ile	Asn	Leu	∨al	Phe 1570	Ile	٧a٦	Leu	Phe	Thr 1575	Gly	Glu	Cys
Val	Leu 1580	Lys	Leu	Ile	Ser	Leu 1585	Arg	Tyr	Tyr	Tyr	Phe 1590	Thr	Ile	Gly
Trp	Asn 1595	Ile	Phe	Asp	Phe	∨al 1600	val	٧a٦	Ile	Leu	ser 1605	Ile	٧a٦	Glу
Met	Phe 1610	Leu	Ala	Glu	Leu	Ile 1615	Glu	Lys	Tyr	Phe	Val 1620	Ser	Pro	Thr
Leu	Phe 1625	Arg	٧a٦	Ile	Arg	Leu 1630	Ala	Arg	Ile	Gly	Arg 1635	Ile	Leu	Arg
Leu	Ile 1640	Lys	Gly	Ala	Lys	Gly 1645	Ile	Arg	Thr	Leu	Leu 1650	Phe	Ala	Leu
Met	Met 1655	Ser	Leu	Pro	Ala	Leu 1660	Phe	Asn	Ile	Gly	Leu 1665	Leu	Leu	Phe
Leu	Val 1670	Met	Phe	Ile	Tyr	Ala 1675	Ile	Phe	Glу	Met	Ser 1680	Asn	Phe	Ala
Tyr	Val 1685	Lys	Arg	Glu	Val	Gly 1690	Ile	Asp	Asp	Met	Phe 1695	Asn	Phe	Glu
Thr	Phe 1700	GТу	Asn	Ser	Met	Ile 1705	Cys		Phe age 1		Ile 1710	Thr	Thr	Ser
									ر	=				

SSCP Update Sequences.ST25

Ala	Gly 1715	Trp	Asp	Gly	Leu	Leu 1720	Ala	Pro	Ile	Leu	Asn 1725	Ser	Gly	Pro
Pro	Asp 1730	Cys	Asp	Pro	Asp	Lys 1735	Asp	His	Pro	Gly	ser 1740	Ser	Val	Lys
Glу	Asp 1745	Cys	Gly	Asn	Pro	ser 1750	٧al	Gly	Ile	Phe	Phe 1755	Phe	Val	Ser
Tyr	Ile 1760	Ile	Ile	Ser	Phe	Leu 1765	Val	Val	Leu	Asn	Met 1770	Tyr	Ile	Ala
٧al	Ile 1775	Leu	Glu	Asn	Phe	Ser 1780	٧a٦	Ala	Thr	Glu	Glu 1785	Ser	Ala	Glu
Pro	Leu 1790	Ser	Glu	Asp	Asp	Phe 1795	Glu	Met	Phe	Tyr	Glu 1800	٧a٦	Trp	Glu
Lys	Phe 1805	Asp	Pro	Asp	Ala	Thr 1810	Gln	Phe	Ile	Glu	Phe 1815	Ala	Lys	Leu
Ser	Asp 1820	Phe.	Ala	Asp	Ala	Leu 1825	Asp	Pro	Pro	Leu	Leu 1830	Ile	Ala	Lys
Pro	Asn 1835	Lys	٧al	Gไn	Leu	Ile 1840	Ala	Met	Asp	Leu	Pro 1845	Met	Val	Ser
Glу	Asp 1850	Arg	Ile	His	Cys	Leu 1855	Asp	Ile	Leu	Phe	Ala 1860	Phe	Thr	Lys
Arg	Val 1865	Leu	Gly	Glu	Ser	Gly 1870	Glu	Met	Asp	Аlа	Leu 1875	Arg	Ile	Gln
Met	Glu 1880	Glu	Arg	Phe	Met	Ala 1885	Ser	Asn	Pro	Ser	Lys 1890	Val	Ser	Tyr
Glu	Pro 1895	Ile	Thr	Thr	Thr	Leu 1900	Lys	Arg	Lys	Gln	Glu 1905	Glu	٧a٦	Ser
Аlа	Ile 1910	Ile	Ile	Gln	Arg	Ala 1915	Tyr	Arg	Arg	Tyr	Leu 1920	Leu	Lys	Gln
Lys	Val 1925	Lys	Lys	۷al	Ser	Ser 1930	Ile	Tyr	Lys	Lys	Asp 1935	Lys	Gly	Lys
Glu	Cys 1940	Asp	Gly	Thr	Pro	Ile 1945	Lys	Glu	Asp	Thr	Leu 1950	Ile	Asp	Lys
Leu	Asn 1955	Glu	Asn	Ser	Thr	Pro 1960	Glu		Thr age 1		Met 1965	Thr	Pro	Ser

## SSCP Update Sequences.ST25

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Phe Glu Lys Asp Lys . Ser Glu Lys Glu Asp Lys Gly Lys 1990 1995 Glu Lys

Asp Ile Arg Glu Ser Lys Lys 2000 2005

85

<210> <211> 2005

PRT

Homo sapiens

<400>

Met Ala Gln Ser Val Leu Val Pro Pro Gly Pro Asp Ser Phe Arg Phe 1 5 10 15

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Gln Arg Ile Ala Glu Glu 20 25 30

Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Asp Glu Asn 35 40 45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe 50 60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp 65 70 75 80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys 90 95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu 100 105 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His 115 120 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val 130 135 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr 145 150 155 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala 165 170 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn 180 185 190

SSCP Update Sequences.ST25

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val 195 200 205 Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala 210 215 Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala 225 230 235 240 Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val 245 250 255 Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly 260 265 270 Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe 275 280 285 Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly 290 295 300 Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile 305 310 315 320 Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu 325 330 335 Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile 340 345 350 Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp 355 360 365 Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp 370 375 Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr 385 390 . 400 Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu 405 410 415Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn 420 425 Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln 435 440 Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala 450 455 460

SSCP Update Sequences.ST25

Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile 465 470 475 480 Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys 485 490 495 Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Gln Lys Glu 500 505 510 Gln Ser Gly Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser 515 520 525 Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser 530 540 Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu 545 550 550 560 Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser 565 570 575 Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp 580 585 590 Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg 595 600 Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn 610 615 620 Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met 625 630 635 Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu 645 650 655 Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu 660 670 Gly Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Tyr 675 680 His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala 690 695 700 Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu 705 710 715 720 Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys 725 730 735

SSCP Update Sequences.ST25

Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val 740 745 750 Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys 755 760 765 Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr 770 780 Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly 785 790 795 800 Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr 805 810 Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser 820 825 830 Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val 835 840 845 Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp 850 860 Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala 865 870 880 Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala 885 890 895 Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys 900 905 910 Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe 915 920 925 Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile 930 940 Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu 945 950 955 960 Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn 965 970 975 Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala 980 985 990 Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Ile Gln Ile Ala Val Gly 995 1000 1005

SSCP Update Sequences.ST25

Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu 1010 1020 Phe Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu 1025 1030 1035 Ile Lys Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile 1040 1045 1050 Ser Asn His Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu Lys Asp Gly Asn Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu Lys Tyr Val Val Asp Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser Ser Glu Ser Asp Met Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser Ser Glu Gly 1130 1135 1140 Ser Thr Val Asp Ile Gly Ala Pro Ala Glu Gly Glu Gln Pro Glu Val Glu Pro Glu Glu Ser Leu Glu Pro Glu Ala Cys Phe Thr Glu 1160 Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile Ser Ile Glu Glu Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr Cys Tyr Lys 1190 1200 Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Glu Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val 1235 1240 1245

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Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala

SSCP Update Sequences.ST25

Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala 1280 1285 1290 Leu Gly Tyr Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu 1295 Arg Ala Leu Arg Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met 1310 1315 Arg Val Val Asn Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys Ile Asn 1355 1360 1365 Tyr Thr Thr Gly Glu Met Phe Asp Val Ser Val Val Asn Asn Tyr 1370 1375 1380 Ser Glu Cys Lys Ala Leu Ile Glu Ser Asn Gln Thr Ala Arg Trp 1385 1390 1395 Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met 1415 Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr 1430 1440 Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile 1465 1470 Phe Gly Phe Asn Gln Gln Lys Lys Phe Gly Gly Gln Asp Ile Asp Asn Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys 1490 1500 Leu Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn 1505 1510 1515 1510

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SSCP Update Sequences.ST25

Lys Phe Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe 1520

Asp Ile Ser Ile Met Ile Leu 1540

Leu 1540

Leu 1540

Leu 1545

Met Val Glu Thr Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu 1550 1560

Tyr Trp Ile Asn Leu Val Phe Ile Val Leu Phe Thr Gly Glu Cys 1565 1570 1575

Val Leu Lys Leu Ile Ser Leu Arg Tyr Tyr Phe Thr Ile Gly 1580 1585 1590

Trp Asn Ile Phe Asp Phe Val Val Ile Leu Ser Ile Val Gly 1595 1600

Met Phe Leu Ala Glu Leu Ile Glu Lys Tyr Phe Val Ser Pro Thr 1610 1620

Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg 1625 1630 1635

Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu 1640 1650

Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe 1655 1660 1665

Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala 1670 1680

Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn Phe Glu 1685 1690 1695

Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser 1700 1710

Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro 1715 1720 1725

Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys 1730 1740

Gly Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser

Tyr Ile Ile Ile Ser Phe Leu Val Val Leu Asn Met Tyr Ile Ala 1760 1765 1770

SSCP Update Sequences.ST25

Val Ile Leu Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu 1775 1780 1785

Pro Leu Ser Glu Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu 1790 1800

Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu 1805 1810

Ser Asp Phe Ala Asp Ala Leu Asp Pro Pro Leu Leu Ile Ala Lys 1820 1830

Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met Val Ser 1835 1840

Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr Lys 1850 1860

Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln 1865 1870

Met Glu Glu Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr 1880 1890

Glu Pro Ile Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser 1895 1900 1905

Ala Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu Leu Lys Gln 1910 1915 1920

Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys Gly Lys 1925 1930 1935

Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp Lys 1940 1950

Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser 1955 1960 1965

Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys 1970 1980

Glu Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys 1985 1990 1995

Asp Ile Arg Glu Ser Lys Lys 2000 2005

<210> 86 <211> 2005 <212> PRT

SSCP Update Sequences.ST25

<213> Homo sapiens

<400> 86

Met Ala Gln Ser Val Leu Val Pro Pro Gly Pro Asp Ser Phe Arg Phe  $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ 

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Gln Arg Ile Ala Glu Glu 20 25 30

Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Glu Asp 40 45

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp 65 70 75 80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys 85 90 95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu 100 105 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His 115 120 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val 130 135 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr 145 150 155 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala 165 170 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn 180 185 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val 195 200 205

Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala 210 215 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala 225 230 235 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val 245 250 255

SSCP Update Sequences.ST25
Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly
260 265 270 Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe 275 280 285 Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly 290 295 300 Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile 305 310 315 320 Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu 325 330 335 Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile  $340 \hspace{1cm} 345 \hspace{1cm} \underline{\hspace{1cm}} 350$ Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp 355 360 365 Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp 370 375 Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr 385 390 395 400 Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu 405 410 415 Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn 420 425 430 Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln 435 440 Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala 450 455 460 Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile 465 470 475 480 Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys 485 490 495 Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Gln Lys Glu 500 505 510 Gln Ser Gly Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser 515 520 525

SSCP Update Sequences.ST25
Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser
530 540 Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu 545 550 560 Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser 575 Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp 580 585 Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg 595 600 605 Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn 610 620 Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met 625 630 635 640 Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu 645 650 Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu 660 665 670 Gly Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Tyr 675 680 685 His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala 690 695 700 Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu 705 710 715 720 Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys 725 730 735 Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val 740 745 750 Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys 755 760 765 Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr 770 780 Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly 785 790 795 800

SSCP Update Sequences.ST25

Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr
. 805 810 815

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser 820 825 830

Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val 835 840 845

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp 850 860

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala 865 870 875 880

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala 885 890 895

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys 900 905 910

Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe 915 920 925

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile 930 935 940

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu 945 950 955 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn 965 970 975

Leu Phe Leu Ala Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala 980 985 990

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly 995 1000

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu 1010 1015 1020

Phe Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu 1025 1030 1035

Ile Lys Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile 1040 1045 1050

Ser Asn His Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu 1055 1060 1065

Lys Asp 1070	Gly	Asn	Gly	Thr	SS(	CP U Ser	odate Gly	e Se	quen Gly	ces.s	T25 Ser	Val	Glu
1070					10/5					1080			
Lys Tyr 1085	۷al	Val	Asp	Glu	ser 1090	Asp	Tyr	Met	ser	Phe 1095	Ile	Asn	Asn
Pro Ser 1100		Thr	val	Thr	Val 1105	Pro	Ile	Ala	val	Gly 1110	Glu	ser	Asp
Phe Glu 1115		Leu	Asn	Thr	Glu 1120	Glu	Phe	Ser	ser	Glu 1125	Ser	Asp	Met
Glu Glu 1130		Lys	Glu	Lys	Leu 1135	Asn	АĴа	Thr	Ser	Ser 1140	Ser	Glu	Gly
Ser Thr 1145	۷al	Asp	Ile	Gly	Ala 1150	Pro	дlа	Glu	σΊу	Glu 1155	Gln	Pro	Glu
Val Glu 1160		Glu	Glu	Ser	Leu 1165	Glu	Pro	Glu	Аlа	Cys 1170	Phe	Thr	Glu
Asp Cys 1175	۷al	Arg	Lys	Phe	Lys 1180	Cys	Cys	Gln	Ile	Ser 1185	Ile	Glu	Glu
Gly Lys 1190	Gly	Lys	Leu	Trp	Trp 1195	Asn	Leu	Arg	Lys	Ala 1200	Cys	Tyr	Lys
Ile Val 1205		His	Asn	Trp	Phe 1210	Glu	Thr	Phe	Ile	Va] 1215	Phe	Met	Ile
Leu Leu 1220	Ser	Ser	Gly	Ala	Leu 1225	Ala	Phe	Glu	Asp	Ile 1230	Tyr	Ile	Glu
Gln Arg 1235					Thr 1240						Asp	Lys	Val
Phe Thr 1250	Tyr	Ile	Phe	Ile	Leu 1255	Glu	Met	Leu	Leu	Lys 1260	Trp	Val	Ala
туг Gly 1265		Gln	Val	Tyr	Phe 1270	Thr	Asn	Ala	Тгр	Cys 1275	Trp	Leu	Asp
Phe Leu 1280		Val	Asp	val	Ser 1285	Leu	val	Ser	Leu	Thr 1290	Ala	Asn	Ala
Leu Gly 1295	Tyr	Ser	Glu	Leu	Gly 1300	Ala	Ile	Lys	Ser	Leu 1305	Arg	Thr	Leu
Arg Ala 1310	Leu	Arg	Pro	Leu	Arg 1315	Αla	Leu	Ser	Arg	Phe 1320	Glu	Gly	Met

SSCP Update Sequences.ST25 Arg Val Val Asn Ala Leu Leu Gly Ala Ile Pro Ser Ile Met 1325 1330 Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile 1340 1345 1350 Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys Ile Asn 1355 Tyr Thr Thr Gly Glu Met Phe Asp Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser Asn Gln Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Leu Gly Tyr Leu 1400 1410 Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr 1430 1440 Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile 1445 1450 1455 Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile 1460 1465 1470 Asp Asn Phe Asn Gln Gln Lys Lys Phe Gly Gln Asp Ile 1475 1480 1485 Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn 1505 1510 1515 Lys Phe Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe 1520 Asp Ile Ser Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu 1550 1560 Tyr Trp Ile Asn Leu Val Phe Ile Val Leu Phe Thr Gly Glu Cys

Val	Leu 1580	Lys	Leu	Ile	Ser	SS Leu 1585	CP U Arg	pdat Tyr	e Se Tyr	quen Tyr	ces.s Phe 1590	T25 Thr	Ile	Gly
Тгр	Asn 1595	Ile	Phe	Asp	Phe	Val 1600	٧a٦	٧a٦	Ile	Leu	Ser 1605	Ile	۷al	Gly
Met	Phe 1610		Ala	Glu	Leu	Ile 1615	Glu	Lys	Tyr	Phe	val 1620	Ser	Pro	Thr
Leu	Phe 1625	Arg	Val	Ile	Arg	Leu 1630	Ala	Arg	Ile	Glу	Arg 1635	Ile	Leu	Arg
Leu	Ile 1640	Lys	Gly	Ala	Lys	Gly 1645	Ile	Arg	Thr	Leu	Leu 1650	Phe	Ala	Leu
Met	Met 1655	Ser	Leu	Pro	Ala	Leu 1660	Phe	Asn	Ile	GТу	Leu 1665	Leu	Leu	Phe
Leu	Val 1670	Met	Phe	Ile	Tyr	Ala 1675	Ile	Phe	Gly	Met	Ser 1680	Asn	Phe	Ala
Tyr	val 1685	Lys	Arg	Glu	٧a٦	Gly 1690	Ile	Asp	Asp	Met	Phe 1695	Asn	Phe	Glu
Thr	Phe 1700	Gly	Asn	Ser	Met	Ile 1705	Cys	Leu	Phe	Gln	Ile 1710	Thr	Thr	Ser
Ala	Gly 1715	Trp	Asp	Glу	Leu	Leu 1720	Ala	Pro	Ile	Leu	Asn 1725	Ser	Gly	Pro
Pro	Asp 1730	Cys	Asp	Pro	Asp	Lys 1735	Asp	нis	Pro	Glу	Ser 1740	Ser	٧a٦	Lys
Gly	Asp 1745	Cys	Glу	Asn	Pro	Ser 1750	val	Glу	Ile	Phe	Phe 1755	Phe	٧a٦	Ser
Tyr	Ile 1760	Ile	Ile	Ser	Phe	Leu 1765	٧a٦	∨al	Leu	Asn	Met 1770	Tyr	Ile	Ala
۷a٦	Ile 1775	Leu	Glu	Asn	Phe	Ser 1780	Val	Аlа	Thr	Glu	Glu 1785	Ser	Αla	Glu
Pro	Leu 1790	Ser	Glu	Asp	Asp	Phe 1795	Glu	Met	Phe	Tyr	Glu 1800	٧al	Trp	Glu
Lys	Phe 1805	Asp	Pro	Asp	ΑΊa	Thr 1810	Gln	Phe	Ile	Glu	Phe 1815	Аlа	Lys	Leu
Ser	Asp 1820	Phe	Αla	Asp	Ala	Leu 1825	Asp	Pro	Pro	Leu	Leu 1830	Ile	Ala	Lys

SSCP Update Sequences.ST25
Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met Val Ser
1835 1840 1845

Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr Lys 1850 1860

Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln 1865 1870 1875

Met Glu Glu Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr · 1880 1885 1890

Glu Pro Ile Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser 1895 1900 1905

Ala Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu Leu Lys Gln 1910 1915 1920

Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys Gly Lys 1925 1930 1935

Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp Lys 1940 1945 1950

Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser 1955 1960 1965

Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys 1970 1980

Glu Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys 1985 1990 1995

Asp Ile Arg Glu Ser Lys Lys 2000 2005

<210> 87

<211> 2005

<212> PRT

<213> Homo sapiens

<400> 87

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Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Gln Arg Ile Ala Glu Glu 20 25 30

Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Glu Asn 35 40 45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe Page 207 55 Update Sequences.ST25 50 55 60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp 70 75 80

PCT/AU2004/001051

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys 85 90 95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu 100 105 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His 115 120 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val 130 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr 145 150 155 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala 165 170 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn 180 185 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val 195 200 205

Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala 210 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala 225 230 235 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val 245 250 255

Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly 260 265 270

Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe 275 280 285

Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly 290 295 300

Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile 305 310 315 320

Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu Page 208 SSCP Update Sequences.ST25 330 335

PCT/AU2004/001051

Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile 340 345 350 Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp 355 360 365 Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp 370 380 Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr 385 390 395 400 Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu 405 410 415 Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn 420 425 430 Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln 435 440 445 Met Leu Glu Gln Leu Lys Lys Gln Glu Glu Ala Gln Ala Ala Ala 450 455 460 Ala Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile 465 470 475 480 Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys 485 490 495 Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Gln Lys Glu 500 505 510 Gln Ser Gly Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser . 525 Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser 530 540 Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu 545 550 560 Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser 565 570 575 Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp 580 585 590 Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg

595

SSCP Update Sequences.ST25 600 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn 610 620 Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met 625 630 635 640 Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu 645 650 655 Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu 660 665 670 Gly Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Tyr 675 680 His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala 690 700 Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Glu Glu 705 710 715 720 Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys 725 730 735 Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val 740 745 750 Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys 755 760 765 Ile Val Leu Asn Thr Leu Phe Met Ála Met Glu His Tyr Pro Met Thr 770 780 Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly 785 790 795 800 Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr 805 810 815 Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser 820 825 Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val 835 840 845 Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp 850 860 Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala Page 210

SSCP Update Sequences.ST25 865 870 875 880

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala 885 890 895

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys 900 905 910

Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe 915 920 925

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile 930 935 940

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu 945 950 955 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn 965 970 975

Leu Phe Leu Ala Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala 980 985

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly 995 1000 1005

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu 1010 1015 1020

Phe Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu 1025 1030 1035

Ile Lys Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile 1040 1045 1050

Ser Asn His Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu 1055 1060 1065

Lys Asp Gly Asn Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu 1070 1080

Lys Tyr Val Val Asp Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn 1085 1090 1095

Pro Ser Leu Thr Val Thr Val Pro Ile Ala Val Gly Glu Ser Asp 1100 1105 1110

Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser Ser Glu Ser Asp Met 1115 1120 1125

Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser Ser Ser Glu Gly Page 211 SSCP Update Sequences.ST25 1135 1140

Ser Thr Val Asp Ile Gly Ala Pro Ala Glu Gly Glu Gln Pro Glu 1145 1150 1155

PCT/AU2004/001051

Val Glu Pro Glu Glu Ser Leu Glu Pro Glu Ala Cys Phe Thr Glu 1160 1170

Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile Ser Ile Glu Glu 1175 1180 1185

Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr Cys Tyr Lys 1190 1200

Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile 1205 1210 1215

Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Glu 1220 1230

Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val 1245 1240 1245

Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Lys Trp Val Ala 1250 1260

Tyr Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp 1265 1270 1275

Phe Leu Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala 1280 1285 1290

Leu Gly Tyr Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu 1295 1300 1305

Arg Ala Leu Arg Pro Leu Arg Ala Leu Ser Gln Phe Glu Gly Met 1310 1320

Arg Val Val Asn Ala Leu Leu Gly Ala Ile Pro Ser Ile Met 1325 1330 1335

Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile Phe Ser Ile 1340 1350 .

Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys Ile Asn 1355 1360 1365

Tyr Thr Thr Gly Glu Met Phe Asp Val Ser Val Val Asn Asn Tyr 1370 1380

Ser Glu Cys Lys Ala Leu Ile Glu Ser Asn Gln Thr Ala Arg Trp Page 212 SSCP Update Sequences.ST25 1385 1390 1395

Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Leu Gly Tyr Leu 1400 1405 1410 Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met 1415 1420 1425 Tyr Ala Ala Val Aṣp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr 1430 1440 Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile 1445 1450 1455 Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile 1460 1465 1470 Asp Asn Phe Asn Gln Gln Lys Lys Phe Gly Gln Asp Ile 1475 1480 1485 Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys 1490 1500 Leu Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn 1505 1510 1515 Lys Phe Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu Tyr Trp Ile Asn Leu Val Phe Ile Val Leu Phe Thr Gly Glu Cys 1565 1570 1575 Val Leu Lys Leu Ile Ser Leu Arg Tyr Tyr Phe Thr Ile Gly 1580 1590 Trp Asn Ile Phe Asp Phe Val Val Ile Leu Ser Ile Val Gly 1600 Met Phe Leu Ala Glu Leu Ile Glu Lys Tyr Phe Val 1610 1615 1620 Ser Pro Thr

Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg

Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu

Page 213

1630

1625

SSCP Update Sequences.ST25 1640 1645 1650

Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala 1670 1680 Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn Phe Glu 1685 1690 1695 Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser 1700 1705 1710 Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys 1730 1740 Gly Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser 1745 1750 1755 Tyr Ile Ile Ser Phe Leu Val Val Leu Asn Met Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala Leu Asp Pro Pro Leu Leu Ile Ala Lys 1820 1830 Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln 1865 1870 Met Glu Glu Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Glu Pro Ile Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser

SSCP Update Sequences.ST25 1895 1900 1905

Ala Ile Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu Leu Lys Gln 1910 1920

Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys Gly Lys 1925 1930 1935

Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp Lys 1940 1945 1950

Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser 1955 1960 1965

Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys 1970 1980

Glu Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys 1985 1990 1995

Asp Ile Arg Glu Ser Lys Lys 2000

<210> 88

<211> 468

<212> PRT

<213> Homo sapiens

<400> 88

Met Ala Ala Arg Gly Ser Gly Pro Arg Ala Leu Arg Leu Leu Leu 1 5 10 15

Val Gln Leu Val Ala Gly Ala Leu Arg Ser Ser Arg Ala Arg Arg Ala 20 25 30

Ala Arg Arg Gly Leu Ser Glu Pro Ser Ser Ile Ala Lys His Glu Asp
45

Ser Leu Leu Lys Asp Leu Phe Gln Asp Tyr Glu Arg Trp Val Arg Pro 50 60

Val Glu His Leu Asn Asp Lys Ile Lys Ile Lys Phe Gly Leu Ala Ile 65 70 75 80

Ser Gln Leu Val Asp Val Asp Glu Lys Asn Gln Leu Met Thr Thr Asn 85 90 95

Val Trp Leu Lys Gln Glu Trp Ile Asp Val Lys Leu Arg Trp Asn Pro 100 105 110

Asp Asp Tyr Gly Gly Ile Lys Val Ile Arg Val Pro Ser Asp Ser Ser 115 120 125 Page 215

SSCP Update Sequences.ST25

Thr Pro Asp Ile Ile Leu Phe Asp Asn Ala Asp Gly Arg Phe Glu 130 140 Gly Thr Ser Thr Lys Thr Val Ile Arg Tyr Asn Gly Thr Val Thr Trp 145 150 155 160 Thr Pro Pro Ala Asn Tyr Lys Ser Ser Cys Thr Ile Asp Val Thr Phe 165 170 175 Phe Pro Phe Asp Leu Gln Asn Cys Ser Met Lys Phe Gly Ser Trp Thr  $180 \,$   $185 \,$  190 Tyr Asp Gly Ser Gln Val Asp Ile Ile Leu Glu Asp Gln Asp Val Asp 195 200 205 Lys Arg Asp Phe Phe Asp Asn Gly Glu Trp Glu Ile Val Ser Ala Thr 210 215 220 Gly Ser Lys Gly Asn Arg Thr Asp Ser Cys Cys Trp Tyr Pro Tyr Val 225 230 235 240 Thr Tyr Ser Phe Val Ile Lys Arg Leu Pro Leu Phe Tyr Thr Leu Phe 245 250 255 Leu Ile Ile Pro Cys Ile Gly Leu Ser Phe Leu Thr Val Leu Val Phe 260 265 270 Tyr Leu Pro Ser Asn Glu Gly Glu Lys Ile Cys Leu Cys Thr Ser Val 275 280 285 Leu Val Ser Leu Thr Val Phe Leu Leu Val Ile Glu Glu Ile Ile Pro 290 295 300 Ser Ser Ser Lys Val Ile Pro Leu Ile Gly Glu Tyr Leu Val Phe Thr 305 310 315 320 Met Ile Phe Val Thr Leu Ser. Ile Met Val Thr Val Phe Ala Ile Asn 325 330 335 Ile His His Arg Ser Ser Ser Thr His Asn Ala Met Ala Pro Leu Val $340 \ \ 345 \ \ 350$ Arg Lys Ile Phe Leu His Thr Leu Pro Lys Leu Leu Ser Met Arg Ser 355 360 365 His Val Asp Arg Tyr Phe Thr Gln Lys Glu Glu Thr Glu Ser Gly Ser 370 375 380 Gly Pro Lys Ser Ser Arg Asn Thr Leu Glu Ala Ala Leu Asp Ser Ile 385 390 395 400 Page 216

#### SSCP Update Sequences.ST25

Arg Tyr Ile Thr Thr His Ile Met Lys Glu Asn Asp Val Arg Glu Val
405 410 415

Val Glu Asp Trp Lys Phe Ile Ala Gln Val Leu Asp Arg Met Phe Leu 420 425 430

Trp Thr Phe Leu Phe Val Ser Ile Val Gly Ser Leu Gly Leu Phe Val 435 440 445

Pro Val Ile Tyr Lys Trp Ala Asn Ile Leu Ile Pro Val His Ile Gly 450 460

Asn Ala Asn Lys 465

<210> 89

<211> 529 <212> PRT

<213> Homo sapiens

<400> 89

Met Gly Pro Ser Cys Pro Val Phe Leu Ser Phe Thr Lys Leu Ser Leu 1 10 15

Trp Trp Leu Leu Thr Pro Ala Gly Gly Glu Glu Ala Lys Arg Pro 20 25 30

Pro Pro Arg Ala Pro Gly Asp Pro Leu Ser Ser Pro Ser Pro Thr Ala 35 40 45

Leu Pro Gln Gly Gly Ser His Thr Glu Thr Glu Asp Arg Leu Phe Lys  $50 \hspace{1.5cm} 55 \hspace{1.5cm} 60$ 

His Leu Phe Arg Gly Tyr Asn Arg Trp Ala Arg Pro Val Pro Asn Thr 65 70 75 80

Ser Asp Val Val Ile Val Arg Phe Gly Leu Ser Ile Ala Gln Leu Ile 85 90 95

Asp Val Asp Glu Lys Asn Gln Met Met Thr Thr Asn Val Trp Leu Lys 100 105 110

Gln Glu Trp Ser Asp Tyr Lys Leu Arg Trp Asn Pro Thr Asp Phe Gly 115 120 125

Asn Ile Thr Ser Leu Arg Val Pro Ser Glu Met Ile Trp Ile Pro Asp 130 135 140

Ile Val Leu Tyr Asn Asn Ala Asp Gly Glu Phe Ala Val Thr His Met 145 150 155 160

SSCP Update Sequences.ST25

Thr Lys Ala His Leu Phe Ser Thr Gly Thr Val His Trp Val Pro Pro 165 170 175 Ala Ile Tyr Lys Ser Ser Cys Ser Ile Asp Val Thr Phe Phe Pro Phe 180 185 190 Asp Gln Gln Asn Cys Lys Met Lys Phe Gly Ser Trp Thr Tyr Asp Lys 195 200 205 Ala Lys Ile Asp Leu Glu Gln Met Glu Gln Thr Val Asp Leu Lys Asp 210 215 Tyr Trp Glu Ser Gly Glu Trp Ala Ile Val Asn Ala Thr Gly Thr Tyr 225 230 235 240 Asn Ser Lys Lys Tyr Asp Cys Cys Ala Glu Ile Tyr Pro Asp Val Thr 245 250 255 Tyr Ala Phe Val Ile Arg Arg Leu Pro Leu Phe Tyr Thr Ile Asn Leu 260 265 270 Ile Ile Pro Cys Leu Leu Ile Ser Cys Leu Thr Val Leu Val Phe Tyr 275 280 285 Leu Pro Ser Asp Cys Gly Glu Lys Ile Thr Leu Cys Ile Ser Val Leu 290 295 300 Leu Ser Leu Thr Val Phe Leu Leu Leu Ile Thr Glu Ile Ile Pro Ser 305 310 315 320 Thr Ser Leu Val Ile Pro Leu Ile Gly Glu Tyr Leu Leu Phe Thr Met 325 330 335 Ile Phe Val Thr Leu Ser Ile Val Ile Thr Val Phe Val Leu Asn Val 340 345 350 His His Arg Ser Pro Ser Thr His Thr Met Pro His Trp Val Arg Gly 355 360 365 Ala Leu Leu Gly Cys Val Pro Arg Trp Leu Leu Met Asn Arg Pro Pro 370 380 Pro Pro Val Glu Leu Cys His Pro Leu Arg Leu Lys Leu Ser Pro 385 390 . 395 Tyr His Trp Leu Glu Ser Asn Val Asp Ala Glu Glu Arg Glu Val Val 405 410 415 Val Glu Glu Asp Arg Trp Ala Cys Ala Gly His Val Ala Pro Ser 420 425 430

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SSCP Update Sequences.ST25

Val Gly Thr Leu Cys Ser His Gly His Leu His Ser Gly Ala Ser Gly 435 440 445

Pro Lys Ala Glu Ala Leu Leu Gln Glu Gly Glu Leu Leu Leu Ser Pro 450 455 460

His Met Gln Lys Ala Leu Glu Gly Val His Tyr Ile Ala Asp His Leu 465 470 475 480

Arg Ser Glu Asp Ala Asp Ser Ser Val Lys Glu Asp Trp Lys Tyr Val 485 490 495

Ala Met Val Ile Asp Arg Ile Phe Leu Trp Leu Phe Ile Ile Val Cys 500 505 510

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Ile

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<211> 505 <212> PRT

<213> Homo sapiens

<400> 90

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Glu Ala Glu His His Leu Phe Glu Arg Leu Phe Glu Asp Tyr Asn Glu 35 40 45

Ile Ile Arg Pro Val Ala Asn Val Ser Asp Pro Val Ile Ile His Phe  $50 \hspace{1cm} 55$ 

Glu Val Ser Met Ser Gln Leu Val Lys Val Asp Glu Val Asn Gln Ile 65 70 75 80

Met Glu Thr Asn Leu Trp Leu Lys Gln Ile Trp Asn Asp Tyr Lys Leu 85 90 95

Lys Trp Asn Pro Ser Asp Tyr Gly Gly Ala Glu Phe Met Arg Val Pro
100 105 110

Ala Gln Lys Ile Trp Lys Pro Asp Ile Val Leu Tyr Asn Asn Ala Val 115 120 125

SSCP Update Sequences.ST25 Gly Asp Phe Gln Val Asp Asp Lys Thr Lys Ala Leu Leu Lys Tyr Thr 130 135 140 Gly Glu Val Thr Trp Ile Pro Pro Ala Ile Phe Lys Ser Ser Cys Lys 145 150 155 160 Ile Asp Val Thr Tyr Phe Pro Phe Asp Tyr Gln Asn Cys Thr Met Lys 165 170 175 Phe Gly Ser Trp Ser Tyr Asp Lys Ala Lys Ile Asp Leu Val Leu Ile . 180 185 190 Gly Ser Ser Met Asn Leu Lys Asp Tyr Trp Glu Ser Gly Glu Trp Ala 195 200 205 Ile Ile Lys Ala Pro Gly Tyr Lys His Asp Ile Lys Tyr Asn Cys Cys 210 215 220 Glu Glu Ile Tyr Pro Asp Ile Thr Tyr Ser Leu Tyr Ile Arg Arg Leu 225 230 240 Pro Leu Phe Tyr Thr Ile Asn Leu Ile Ile Pro Cys Leu Leu Ile Ser 245 250 255 Phe Leu Thr Val Leu Val Phe Tyr Leu Pro Ser Asp Cys Gly Glu Lys 260 265 270 Val Thr Leu Cys Ile Ser Val Leu Leu Ser Leu Thr Val Phe Leu Leu 275 280 285 Val Ile Thr Glu Thr Ile Pro Ser Thr Ser Leu Val Ile Pro Leu Ile 290 295 300 Gly Glu Tyr Leu Leu Phe Thr Met Ile Phe Val Thr Leu Ser Ile Val 305 310 315 320 Ile Thr Val Phe Val Leu Asn Val His Tyr Arg Thr Pro Thr His 325 330 335 Thr Met Pro Ser Trp Val Lys Thr Val Phe Leu Asn Leu Leu Pro Arg 340 345 350 Val Met Phe Met Thr Arg Pro Thr Ser Asn Glu Gly Asn Ala Gln Lys 355 360 365 Pro Arg Pro Leu Tyr Gly Ala Glu Leu Ser Asn Leu Asn Cys Phe Ser 370 375 380 Arg Ala Glu Ser Lys Gly Cys Lys Glu Gly Tyr Pro Cys Gln Asp Gly 385 390 395 400

SSCP Update Sequences.ST25
Met Cys Gly Tyr Cys His His Arg Arg Ile Lys Ile Ser Asn Phe Ser
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Ala Asn Leu Thr Arg Ser Ser Ser Glu Ser Val Asp Ala Val Leu 420 425 430

Ser Leu Ser Ala Leu Ser Pro Glu Ile Lys Glu Ala Ile Gln Ser Val 435 440 445

Lys Tyr Ile Ala Glu Asn Met Lys Ala Gln Asn Glu Ala Lys Glu Ile 450 455 460

Gln Asp Asp Trp Lys Tyr Val Ala Met Val Ile Asp Arg Ile Phe Leu 465 470 475 480

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Gln Pro Leu Met Ala Arg Glu Asp Ala 500 505

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<400> 91

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Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala 50 60

Gly Lys Pro Pro Gln Ala Gln Arg Leu Leu Pro Gln Ala Glu Phe 65 70 75 80

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Arg Leu Arg Val Pro Pro Gly Phe Leu Leu Pro Arg Ala Val Cys Val 100 105 110

Phe His His Gln Gly Val

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<213> Homo sapiens

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Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala 50 55 60

Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe 65 70 75 80

Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His 85 90 95

Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe 100 105 110

Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile 115 120 125

Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg 130 135 140

Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg 150 155 160

Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu 165 170 175

Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe 180 185 190

Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met 195 200 205

Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val 210 215 220

Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe 225 230 235 240

Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly 245 250 255 Page 222

# SSCP Update Sequences.ST25

Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu 260 265 270 Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp 275 280 285 Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe 290 295 300 Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val 305 310 315 320 Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala 325 330 335 Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser 340 345 350 Gly Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr 355 360 365 Val Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser Arg Leu 370 375 380 Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys Ser Lys 385 390 395 400 Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Pro Glu Pro Ser Pro Ser 405 410 415 Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser Pro Arg Gly Val 420 425 430 Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala Gln Thr Val Arg Arg Ser 445 445 Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser Pro Ser Lys Val Pro Lys 450 460 Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln Ala Phe Arg Ile 465 470 475 480 Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala Ser Leu Pro Gly 485 490 495 Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu Phe Val Thr Glu 500 505 510 Asp Leu Thr Pro Gly Leu Lys Val Ser Ile Arg Ala Val Cys Val Met 515 525 Page 223

## SSCP Update Sequences.ST25

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SSCP Update Sequences.ST25

Ser Cys Tyr Ala Ala Val Ala Pro Cys Ala Lys Val Arg Pro Tyr Ile 805 810 815

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Trp Ala Gly Pro Arg Lys 850

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<211> 429 <212> PRT

<213> Homo sapiens

<400> 93

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Glu Lys Lys Leu Lys Val Gly Phe Val Gly Leu Asp Pro Gly Ala Pro 20 25 30

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Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala 50 60

Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe 65 70 75 80

Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His 85 90 95

Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe 100 105 110

Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile 115 120 125

Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg 130 140

Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg 145 150 155 160

Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu 165 170 175

SSCP Update Sequences.ST25

Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe 180 185 190

Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met 195 200 205

Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val 210 215 220

Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe 225 230 235 240

Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly 245 250 255

Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu 260 265 270

Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp 275 280 285

Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe 290 295 300

Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val 305 310 315 320

Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala 325 330 335

Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser 340 345 350

Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr 355 360 365

Val Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser Arg Leu 370 380

Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys Ser Lys 385 390 395 400

Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Pro Glu Pro Ser Pro Ser 405 410 415

Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser Pro 420 425

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<211> 854

<212> PRT

SSCP Update Sequences.ST25

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<400> 94

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Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala 50 60

Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe 65 70 75 80

Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His 85 90 95

Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe 100 105 · 110

Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile 115 120 125

Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg 130 135 140

Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg 145 150 155 160

Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu 165 170 175

Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe 180 185 190

Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met 195 200 205

Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val 210 220

Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe 225 230 235 240

Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly 245 250 255

SSCP Update Sequences.ST25
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260 265 270 Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp 275 . 280 285 Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe 290 300 Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val 305 310 315 320 Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala 325 330 335 Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser 340 345 350 Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr 355 360 365 Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser Arg Leu 370 380 Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys Ser Lys 385 390 395 400 Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Glu Pro Ser Pro Ser 410 415Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser Pro Arg Gly Val 420 425 430 Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala Gln Thr Val Arg Arg Ser 440 445 Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser Pro Ser Lys Val Pro Lys 450 460 Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln Ala Phe Arg Ile 465 470 480 Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala Ser Leu Pro Gly 485 490 495 Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu Phe Val Thr Glu 500 505 Asp Leu Thr Pro Gly Leu Lys Val Ser Ile Arg Ala Val Cys Val Met 515 520 525

SSCP Update Sequences.ST25
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Pro Pro Pro Arg Ser Ala Thr Gly Glu Gly Pro Phe Gly Asp Val Gly 835 840 845

Trp Ala Gly Pro Arg Lys 850

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<211> 854

<212> PRT <213> Homo sapiens

<400> 95

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Asp Ser Thr Arg Asp Gly Ala Leu Leu Ile Ala Gly Ser Glu Ala Pro 35 40 45

Lys Arg Gly Ser Ile Leu Ser Lys Pro Arg Ala Gly Gly Ala Gly Ala 50 55 60

Gly Lys Pro Pro Lys Arg Asn Ala Phe Tyr Arg Lys Leu Gln Asn Phe 65 70 75 80

Leu Tyr Asn Val Leu Glu Arg Pro Arg Gly Trp Ala Phe Ile Tyr His 85 90 95

Ala Tyr Val Phe Leu Leu Val Phe Ser Cys Leu Val Leu Ser Val Phe 100 105 110

Ser Thr Ile Lys Glu Tyr Glu Lys Ser Ser Glu Gly Ala Leu Tyr Ile 115 120 125

Leu Glu Ile Val Thr Ile Val Val Phe Gly Val Glu Tyr Phe Val Arg 130 135 140

Ile Trp Ala Ala Gly Cys Cys Cys Arg Tyr Arg Gly Trp Arg Gly Arg 145 150 155 160

Leu Lys Phe Ala Arg Lys Pro Phe Cys Val Ile Asp Ile Met Val Leu 165 170 175

Ile Ala Ser Ile Ala Val Leu Ala Ala Gly Ser Gln Gly Asn Val Phe Page 230 WO 2005/014863

SSCP Update Sequences.ST25 180 185 190 PCT/AU2004/001051

Ala Thr Ser Ala Leu Arg Ser Leu Arg Phe Leu Gln Ile Leu Arg Met 195 200 205 Ile Arg Met Asp Arg Arg Gly Gly Thr Trp Lys Leu Leu Gly Ser Val 210 220 Val Tyr Ala His Ser Lys Glu Leu Val Thr Ala Trp Tyr Ile Gly Phe 225 230 235 Leu Cys Leu Ile Leu Ala Ser Phe Leu Val Tyr Leu Ala Glu Lys Gly 245 250 255 Glu Asn Asp His Phe Asp Thr Tyr Ala Asp Ala Leu Trp Trp Gly Leu 260 265 270 Ile Thr Leu Thr Thr Ile Gly Tyr Gly Asp Lys Tyr Pro Gln Thr Trp 275 280 285 Asn Gly Arg Leu Leu Ala Ala Thr Phe Thr Leu Ile Gly Val Ser Phe 290 300 Phe Ala Leu Pro Ala Gly Ile Leu Gly Ser Gly Phe Ala Leu Lys Val 305 310 315 Gln Glu Gln His Arg Gln Lys His Phe Glu Lys Arg Arg Asn Pro Ala 325 330 335 Ala Gly Leu Ile Gln Ser Ala Trp Arg Phe Tyr Ala Thr Asn Leu Ser 340 345 350Arg Thr Asp Leu His Ser Thr Trp Gln Tyr Tyr Glu Arg Thr Val Thr 355 360 365 Val Pro Met Tyr Ser Ser Gln Thr Gln Thr Tyr Gly Ala Ser Arg Leu 370 380 Ile Pro Pro Leu Asn Gln Leu Glu Leu Leu Arg Asn Leu Lys Ser Lys 385 390 395 400 Ser Gly Leu Ala Phe Arg Lys Asp Pro Pro Pro Glu Pro Ser Pro Ser 405 410 415 Gln Lys Val Ser Leu Lys Asp Arg Val Phe Ser Ser Pro Arg Gly Val 420 425 430 Ala Ala Lys Gly Lys Gly Ser Pro Gln Ala Gln Thr Val Arg Arg Ser 445 Pro Ser Ala Asp Gln Ser Leu Glu Asp Ser Pro Ser Lys Val Pro Lys Page 231

SSCP Update Sequences.ST25 450 455 460

Ser Trp Ser Phe Gly Asp Arg Ser Arg Ala Arg Gln Ala Phe Arg Ile 465 470 475 480 Lys Gly Ala Ala Ser Arg Gln Asn Ser Glu Glu Ala Ser Leu Pro Gly
485 490 495 Glu Asp Ile Val Asp Asp Lys Ser Cys Pro Cys Glu Phe Val Thr Glu 500 505 Asp Leu Thr Pro Gly Leu Lys Val Ser Ile Arg Ala Val Cys Val Met 515 520 525 Arg Phe Leu Val Ser Lys Arg Lys Phe Lys Glu Ser Leu Arg Pro Tyr 530 540 Asp Val Met Asp Val Ile Glu Gln Tyr Ser Ala Gly His Leu Asp Met 545 550 555 560 Leu Ser Arg Ile Lys Ser Leu Gln Ser Arg Val Asp Gln Ile Val Gly 565 570 Arg Gly Pro Ala Ile Thr Asp Lys Asp Arg Thr Lys Gly Pro Ala Glu 580 585 590 Ala Glu Leu Pro Glu Asp Pro Ser Met Met Gly Arg Leu Gly Lys Val 595 600 605 Glu Lys Gln Val Leu Ser Met Glu Lys Lys Arg Asp Phe Leu Val Asn 610 620 Ile Tyr Met Gln Arg Met Gly Ile Pro Pro Thr Glu Thr Glu Ala Tyr 625 630 635 Phe Gly Ala Lys Glu Pro Glu Pro Ala Pro Pro Tyr His Ser Pro Glu 645 650 655 Asp Ser Arg Glu His Val Asp Arg His Gly Cys Ile Val Lys Ile Val 660 665 670 Arg Ser Ser Ser Thr Gly Gln Lys Asn Phe Ser Ala Pro Pro Ala 675 680 Ala Pro Pro Val Gln Cys Pro Pro Ser Thr Ser Trp Gln Pro Gln Ser 690 695 700 His Pro Arg Gln Gly His Gly Thr Ser Pro Val Gly Asp His Gly Ser 705 710 715 720 Leu Val Arg Ile Pro Pro Pro Pro Ala His Glu Arg Ser Leu Ser Ala Page 232

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SSCP Update Sequences.ST25 730

Tyr Gly Gly Asn Arg Ala Ser Met Glu Phe Leu Arg Gln Glu Asp 740 745 750

Thr Pro Gly Cys Arg Pro Pro Glu Gly Thr Leu Arg Asp Ser Asp Thr 755 760 765

Ser Ile Ser Ile Pro Ser Val Asp His Glu Glu Leu Glu Arg Ser Phe 770 780

Ser Gly Phe Ser Ile Ser Gln Ser Lys Glu Asn Leu Asp Ala Leu Asn 785 790 795 800

Ser Cys Tyr Ala Ala Val Ala Pro Cys Ala Lys Val Arg Pro Tyr Ile 805 810 815

Ala Glu Gly Glu Ser Asp Thr Asp Ser Asp Leu Cys Thr Pro Cys Gly 820 825

Pro Pro Pro Arg Ser Ala Thr Gly Glu Gly Pro Phe Gly Asp Val Gly 835 840 845

Trp Ala Gly Pro Arg Lys 850

International application No.

PCT/AU2004/001051

Α.	CLASSIFICATION OF SUBJECT MAT	TER						
Int. Cl. 7:	C12Q 1/68, C12N 15/01, A61K 39/3	95 CC	07K14/47					
According to I	International Patent Classification (IPC)	or to bo	oth national classification and IPC					
В.	FIELDS SEARCHED							
See electroni								
See electroni	c databases		extent that such documents are included in the fields searc	hed				
Electronic data WPIDS, CA	base consulted during the international search Medline. SCN1A, polymorphism/m	n (name utatior	of data base and, where practicable, search terms used) n/SNP, epilepsy/disease/febrile seizure					
C. DOCUMENTS CONSIDERED TO BE RELEVANT								
Category*	Citation of document, with indication,	where a	appropriate, of the relevant passages	Relevant to claim No.				
. ·			annel $\alpha$ subunit type 1 (SCN1A) in intractable alized tonic-clonic seizures. Brain, 2003.					
A	Nabbout R et al. Spectrum of SCN1A mutations in severe myoclonic epilepsy of infancy. Neurology, 2003 Jun 24. 60(12):1961-7.							
A	WO 2003/008574 A1 (BIONOMICS LIMITED) 30 January 2003							
A	WO 2002/06521 A1 (BIONOMICS LIMITED) 24 January 2002							
<b>A</b>	WO 2002/50096 A1 ((BIONOMICS LIMITED) 27 June 2002							
Further documents are listed in the continuation of Box C X See patent family annex								
"A" documen	ategories of cited documents: t defining the general state of the art which is dered to be of particular relevance	"T"	later document published after the international filing date or pr conflict with the application but cited to understand the princip underlying the invention	iority date and not in le or theory				
•	arlier application or patent but published on or after the nternational filing date		document of particular relevance; the claimed invention cannot or cannot be considered to involve an inventive step when the calone					
or which	L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art					
"O" document referring to an oral disclosure, use, exhibition or other means		"&"	document member of the same patent family					
	t published prior to the international filing date than the priority date claimed							
	al completion of the international search		Date of mailing of the international search report					
28 September 2004  Name and mailing address of the ISA/AU			7 OCT 2004 Authorized officer					
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au			Gillian Allen					
Facsimile No. (	02) 0283 3929	Telephone No : (02) 6283 2266						

International application No.

PCT/AU2004/001051

Box No. I	Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)						
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:							
1.	Claims Nos.:						
	because they relate to subject matter not required to be searched by this Authority, namely:						
	$\cdot$						
2. X	Claims No 65 and 66						
2. 22	because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:						
	The scope of these claims is so unclear that no meaningful search can be performed.						
3.	Claims Nos.:						
	because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)						
Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)							
This Intern	ational Searching Authority found multiple inventions in this international application, as follows:						
The IS	A found that the claims were directed to multiple invention						
See Su	pplemental Box III for details						
500 54	ppromonal 20% III for details						
1.	As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.						
2	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.						
3.	As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:						
•							
4. X	No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by:						
	Claims 1-16 19-27, 29-64, 67-85 in so far as they are directed to polymorphisms in SCN1A						
	$\cdot$						
Remark on	Protest The additional search fees were accompanied by the applicant's protest.						
	No protest accompanied the payment of additional search fees.						

International application No.

PCT/AU2004/001051

## Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

# Continuation of Box No: III

The present claims are to 72 different mutations in 18 different ion channel genes, the mutant genes and their encoded polypeptides and antibodies thereto, and to uses of these in diagnosis or therapy.

The unifying feature of the claimed inventions is a disease-associated mutation of an ion channel gene. However, ion channel disease-associated mutations are known for every one of the ion channels of the claims, ie SCN, CHRN, KCQN, and GABR.

Therefore, since the unifying feature of the different mutations is not novel, it cannot be accepted as a special technical feature that would unite the claims.

There are therefore 72 separate inventions claimed.

However, this office believes that all claimed mutations of any one of the claimed genes could be searched without undue effort, and has chose to search the claims in so far as they are directed to polymorphisms of SCN1A

International application No.

PCT/AU2004/001051

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	P	atent Family Member	
WO 2003/008574	CA 2454073	:	
	EP 1407013		
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	US 2004110706		
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX